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ELEMENTS OF

PHYSIOLOGY

FOR STUDENTS OF MEDICINE AND ADVANCED BIOLOGY

BY

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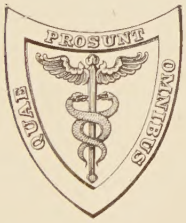

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PREFACE.

In this book the subject of Physiology is presented by development of two key-principles. The first of these is the familiar key-principle of general physiology, namely that living protoplasm is a system of molecules and ions, hence understanding of its structure and functioning is to be sought by attempting to apply to it the physical, physico-chemical and chemical laws by which the interrelations of molecules and ions are described. The first section of the book contains an account of the nature and capacities of protoplasm as revealed by observation and experimentation, together with such interpretations as the laws referred to above appear to permit at the present time.

The second key-principle is that every protoplasmic cell is inherently a self-sustaining system. Consequently, if it is continuously provided with a proper environment, it should continue to live and function indefinitely (subject, of course, to the possible influence of intrinsic senility). In accordance with this principle, the task of Physiology after the properties of protoplasm have been examined, is to enquire what are the factors of suitable cell environment, and what are the permissible limits of departure from the optimum for each. The second section deals with this problem.

In a highly organized body, like that of man, the maintenance of proper cell-environment depends on the interaction of various complex mechanisms. The third section is concerned with these.

Since bodily maintenance must be carried on in the presence of a changing external environment various adjustments of the organism as a whole are necessary. The fourth section considers how these are achieved. A final chapter on Reproduction deals with the transmission of the protoplasmic continuum from generation to generation.

We hold strongly to the view that students of Physiology should form the habit of looking beyond their textbooks to authoritative

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monographic reviews and, so far as time permits, to original experimental publications. In terms of this view the textbook takes on two main functions: (1) To present concisely and clearly those elementary facts and principles of Physiology which every qualified student of the subject should have at command; (2) to refer at each step in the development to readily accessible monographs and bibliographies dealing with the matter under discussion. Fortunately for English-speaking students of Physiology these are now available in most of the important fields both of Physiology and of the sciences to which it is closely related.

In accordance with the above view of the function of a textbook of Physiology we have adopted a plan of drastic selection of material, attempting, so far as we are able, to limit the presentation to such facts and principles as are fundamental to an adequate grasp of Physiology as a whole, and indicating by carefully chosen bibliographic references sources to which the student may turn if his interest is aroused, as we hope it may be, to pursue individual topics further. We have departed from this principle to some extent in the chapters dealing with Hearing and Vision; chiefly for the reason that much of the recent progress in these fields has been in laboratories devoted to sound transmission and reproduction on the one hand and to illumination as a problem in engineering on the other. The literature from these laboratories appears less likely to become familiar to most students of Physiology than the literature of other fields, consequently a fuller treatment in the textbook seems justified.

Our policy in the matter of mentioning investigators by name in the text has been dictated by the desire to facilitate the work of the student rather than to do honor to particular scientific workers. We have given preference in the bibliographies at the ends of the chapters to monographic reviews wherever possible. The mention of individuals in the text is intended to direct the attention of the reader without loss of time to the portion of a review bearing directly on the topic in hand. The very recent contributions are both referred to by the names of the authors and listed individually in the bibliographies.

We appreciate keenly the heavy responsibility we have incurred in omitting altogether many important data of Physiology and in giving others only brief mention, while elaborating still others fairly extensively. We realize also that errors of description and

interpretation have probably been made in spite of our best efforts to avoid them. We welcome comments from our colleagues in reference both to our selection of material and to our treatment of what we have selected.

The acknowledgment of aid received presents considerable difficulties. Authors of general textbooks realize very early in their labors how deeply they are indebted to the whole body of workers both in the field of their authorship and in related fields as well. More immediate is their indebtedness to those who have prepared reviews and bibliographies dealing with particular phases of the subject. The papers in *Physiological Reviews* have been of outstanding usefulness to us, as have been also the *Harvey Lectures, die Ergebnisse der Physiologie,* and the several separate monographs on Physiology and Biochemistry. We have also profited by the labors of other authors of textbooks. The monumental work of Bayliss has been particularly helpful and inspiring. Our colleagues at Stanford, particularly Messrs. Baumberger, Field, Hall, Irving, Shafer and Slonaker of the department of Physiology, Dr. W. R. Miles of the department of Psychology, and Dr. C. L. Alsberg of the Food Research Institute, have helped in various ways, notably by calling our attention to references we might otherwise have missed. The Senior author profited greatly from discussions with his former colleagues at Harvard, and also with his colleagues for a brief period in the department of Physiology at the University of Toronto. Miss Mary Evelyn Kay has given invaluable aid, particularly in the preparation of the index, and Mr. Richard Hubbard has made all the drawings original with us or modified by us from other sources. Cuts adopted without change are acknowledged as to origin individually in the text.

E. G. M.,
F. W. W.

Stanford University, California,
1928.

CONTENTS.

PART I.

THE NATURE AND CAPACITIES OF PROTOPLASM (E. G. M.).

CHAPTER I.

THE PHYSICO-CHEMICAL ORGANIZATION OF PROTOPLASM

Protoplasm 17
Micellæ 21
Hydrogen-ion Concentration 24
Donnan Equilibrium 27
Surface Energy 29
Brownian Movement 30
Osmotic Pressure 30
Summary 33
Bibliography 34

CHAPTER II.

CELL STRUCTURE AND THE CELL MEMBRANE

Cell Membrane 35
Membrane Permeability 37
Cell Structure 40
Summary 43
Bibliography 45

CHAPTER III.

METABOLISM: THE CHEMISTRY OF THE LIFE PROCESSES

Metabolism 46
Biological Oxidation 48
Enzymes 53
Vitamins and Hormones 55
Summary 57
Bibliography 58

CHAPTER IV.

METABOLISM: THE CAPACITIES OF PROTOPLASM

Basic Metabolism 59
Growth Metabolism 61
Functional Metabolism 65
Summary 66
Bibliography 68

CHAPTER V.

Stimulation: The Control of Function

Irritability and Stimulation 69
Classes of Stimuli 70
Nervous Stimulation 74
Inhibition 75
Receptors 76
Summary 76
Bibliography 77

CHAPTER VI.

Contraction

Amœboid Movement 78
Ciliary Motion 78
Structure of Skeletal Muscle Fiber 79
Isotonic and Isometric Contraction 82
Muscle, a Chemical Engine 83
Smooth Muscle 92
Cardiac Muscle 94
Summary 96
Bibliography 99

CHAPTER VII.

Conduction

Conduction an Important Property of Protoplasm 100
Nerve Cells and the Nerve Net 100
The Neuron 101
Bases for Study of the Nervous System 104
The Nerve Impulse 106
Functional Metabolism in Nerve Trunks 107
The Propagated Disturbance 109
Velocity of Nerve Impulses 109
Special Properties of Synapses 112
Functions of the Cell Body 115
Summary 116
Bibliography 119

CHAPTER VIII.

Simple and Complex Reflex Action: The Autonomic Nervous System

The Simple Reflex 120
Complex Reflexes 127
The Autonomic System 128
Summary 132
Bibliography 133

CHAPTER IX.

GLAND FUNCTION: THE MANUFACTURE AND OUTPOURING OF MATERIAL

The Secretory Process 135
Serous and Mucous Cells 138
Zymogen and Mucinogen Granules 139
Secretion Under Hormone Stimulation 140
Secretion of Hydrochloric Acid 141
Tear Glands 142
Sweat Glands 142
The Kidney Tubule 143
Sebaceous Secretion 148
Endocrine Glands 149
Summary 149
Bibliography 152

PART II.

CELL ENVIRONMENT (E. G. M.).

CHAPTER X.

CELL ENVIRONMENT: TEMPERATURE; WATER CONTENT; HYDROGEN-ION CONCENTRATION

Temperature 154
Water Content 157
Hydrogen-ion Concentration 160
Summary 167
Bibliography 171

CHAPTER XI.

CELL ENVIRONMENT: INORGANIC SALTS; NUTRIENTS

Inorganic Salts Essential to Protoplasm 172
Nutrients 175
Summary 189
Bibliography 192

CHAPTER XII.

CELL ENVIRONMENT: VITAMINS AND HORMONES

Vitamins 193
Hormones 197
Summary 209
Bibliography 213

CHAPTER XIII.

CELL ENVIRONMENT: OXYGEN

Hemoglobin as Oxygen Carrier 215
Anoxemia 221
The Effects of High Alveolar Pressures 225
Summary 226
Bibliography 228

CHAPTER XIV.

CELL ENVIRONMENT: MISCELLANEOUS METABOLITES

Metabolites as Factors Influencing Metabolism 229
Insoluble Metabolites 229
Soluble Non-nitrogenous Metabolites 231
Nitrogenous Metabolites 235
Summary 241
Bibliography 243

PART III.

BODILY MAINTENANCE (E. G. M.).

CHAPTER XV.

THE MAINTENANCE OF CELL ENVIRONMENT IN VERTEBRATES

Bodily Maintenance 247
Summary 248

CHAPTER XVI.

BLOOD: PLASMA AND CORPUSCLES

Blood Plasma 250
Immunizing Agencies 252
Blood Cells 258
Blood Platelets 263
Blood as a Physico-chemical System 263
Summary 265
Bibliography 268

CHAPTER XVII.

BLOOD: QUANTITY; CLOTTING; TRANSFUSION

Quantity of Blood 269
Blood Clotting 273
Blood Transfusion 279
Summary 280
Bibliography 282

CHAPTER XVIII.

CIRCULATION: VOLUME; CIRCULATORY APPARATUS; HEART

Unit Circulation 283
Subdivisions of the Circulatory Apparatus 286
The Heart 290
Nervous Regulation of Cardiac Activity 299
Functions of the Cardiac Centers 303
Summary 308
Bibliography 310

CHAPTER XIX.

CIRCULATION: THE CARDIAC CYCLE: VENTRICULAR OUTPUT; CIRCULATION TIME; VELOCITY OF FLOW

The Cardiac Cycle 311
Ventricular Output 318
Circulation Time 320
Velocity of Blood Flow 321
Summary 323
Bibliography 324

CHAPTER XX.

CIRCULATION: ARTERIAL PRESSURE; PULSE; VASOMOTOR MECHANISM

Arterial Pressure 325
The Pulse 330
Function of the Arterioles 333
Summary 338
Bibliography 340

CHAPTER XXI.

CIRCULATION: CAPILLARIES; VENULES; VEINS; SPECIAL FEATURES; LYMPH FLOW

The Capillaries 341
The Venules and Small Veins 343
The Veins 343
Distribution of Blood Flow 347
Circulation Through Special Regions 351
Lymph Flow 357
Cerebrospinal Fluid 359
Summary 360
Bibliography 363

CHAPTER XXII.

THE RESPIRATORY MECHANISM: THE ACT OF BREATHING; MAINTENANCE OF A NORMAL ALVEOLAR ATMOSPHERE

Factors in Lung Ventilation 365
Summary 371
Bibliography 372

CHAPTER XXIII.

The Respiratory Mechanism: The Control of Breathing

The Mechanism of Breathing 373
The Respiratory Center 374
Mechanism of Hyperpnea 375
Mechanism of Dyspnea 376
Lung Ventilation in Exercise 376
Lung Ventilation in Anoxemia 377
Lung Ventilation in Hemorrhage and in Oxygen Excess . . . 378
Asphyxia 378
Effects of Overventilation 379
Intrapulmonary Pressure 382
Intrathoracic Pressure 383
Principles of Ventilation 384
Summary 385
Bibliography 387

CHAPTER XXIV.

The Mechanism of Digestion: Digestion in Mouth and Stomach

Function of the Digestive Apparatus 388
The Digestive Process 388
Mastication 389
The Salivary Glands 389
Deglutition 392
The Disposition of Food in the Stomach 395
Gastric Juice 397
The Emptying of the Stomach 403
Absorption from the Stomach 405
Vomiting 406
Summary 407
Bibliography 410

CHAPTER XXV.

The Mechanism of Digestion: The Small Intestine

Chyme 411
Pancreatic Juice 412
Action of Bile 414
Movements of the Small Intestine 416
Intestinal Juice 418
Bacterial Action in the Small Intestine 419
Absorption from the Small Intestine 420
Summary 422
Bibliography 424

CHAPTER XXVI.

The Mechanism of Digestion: The Large Intestine

The Proximal Colon 425
Autointoxication 426
Food Poisoning 426
Absorption from the Distal Colon 427
Movement of Feces through the Distal Colon 428
Summary 430
Bibliography 431

CHAPTER XXVII.

Excretion

The Kidneys 432
Normal Urine 432
The Ureters 441
The Bladder: Micturition 441
Summary 443
Bibliography 445

CHAPTER XXVIII.

Temperature Regulation

The Heat Center 446
Sweat Secretion 449
Physiological Temperature Rise 450
Fever 451
Summary 451
Bibliography 453

CHAPTER XXIX.

Calorimetry and Dietetics

Basal Metabolism in Relation to Body Surface and Protoplasmic Mass 454
Basal Metabolism 456
Total Metabolism 462
Dietary Fundamentals 464
Nitrogen Equilibrium 465
Optimum Protein Consumption 466
Practical Dietaries 467
Effects of Undernutrition 468
Summary 469
Bibliography 472

PART IV.

EXTERNAL ADJUSTMENT.

CHAPTER XXX.

Receptors: Classification; Significance in Reflex; Relation to Sensation (F. W. W.)

476
Classification of Reactions 479
Classification of Receptors 481
The Stimulus and Its Effects 482
Attributes of Sensations 495
Summary 497
Bibliography . . . . .

CHAPTER XXXI.

The Proprioceptors (F. W. W.)

The Motoceptors 499
The Non-acoustic Labyrinth 504
Summary 509
Bibliography 510

CHAPTER XXXII.

Cutaneous Receptors (F. W. W.)

Temperature Receptors 512
Mechanical Stimulation of the Skin 518
Stimulation of Touch 520
Cutaneous Pain 528
Pain in Deeper Tissues 530
Summary 532
Bibliography 534

CHAPTER XXXIII.

Taste and Smell (F. W. W.)

Taste 536
Smell 539
Summary 544
Bibliography 545

CHAPTER XXXIV.

Hearing (F. W. W.)

Physical Nature of Sound 546
The Receptor for Hearing 551
Reflexes 554
Sensations 555
Localization 562
Voice 564
Speech 566
Functions of the Cochlea 569
Summary 576
Bibliography 578

CHAPTER XXXV.

Vision: Image Formation (F. W. W.)

The Stimulus 580
Anatomical Basis of Image Formation 580
Structure of the Human Eye 581
Development of the Eye 587
Nutrition of the Eye 588
Classification of Structures Involved in Vision and Plan of Treatment . 589
Refraction and Image Formation 590
Image Formation in the Human Eye 603
Focal Defects 613
Iris 619
Pupillary Size 619
Summary 622

CHAPTER XXXVI.

Vision: Sensation (F. W. W.)

The Retina 627
Objective Changes on Stimulation 632
Visual Sensations 634
Brilliance 636
Chromaticity 649
Color-blindness 656
Color Hypotheses 657
Spatial Relations 660
Eye Movements 664
Form 673
Motion 673
Distance 674
Binocular Vision 675
Summary 683
Bibliography 687

CHAPTER XXXVII.

Neuromuscular Functioning: Posture (E. G. M.)

Distribution of Motor Neurons 690
Myoneural Junctions and the Effect of Curare 690
Skeletal Muscle Tonus 691
Decerebrate Rigidity 695
Cerebellar Function 695
Summary 697
Bibliography 698

CHAPTER XXXVIII.

The Cerebrum: General Functions and Connections (E .G. M.)

Delayed Response a Factor in Behavior 699
Distance Receptors and the Brain 699
The Cerebral Cortex 700
Classification of Afferent Paths 702
Sensory Areas of the Cortex 710
Efferent Tracts from the Cortex 712
Significance of Association and Commissural Fibers 714
Summary 714
Bibliography 716

CHAPTER XXXIX.

Cerebral Function: Acquired Reactions: Conditioned Reflexes; Automatisms (E. G. M.)

Mind Considered from the Viewpoint of Physiology 717
Memory 717
Effects of Decortication 720

Acquired Reactions 721
Unconditioned Reflexes 723
Conditioned Reflexes 723
Habits 726
Language 727
Cortical Control of Inherent Reflexes 730
Awareness and Volition 731
Summary 731
Bibliography 733

CHAPTER XL.

Cerebral Function: Affective States; Nervous Fatigue; Sleep (E. G. M.).

Affective States 734
Nervous Fatigue 736
Sleep 738
Waking 742
Summary 743
Bibliography 744

CHAPTER XLI.

Reproduction (E. G. M.).

The Germinal Tissues 745
Maturation 745
Fertilization 746
Factors in Development 747
The Attainment of Sexual Maturity 747
Spermatozoa 749
Insemination 750
Ovogenesis 751
Ovulation 752
Menstruation 755
The Reproductive Cycle in the Absence of Pregnancy 756
Conception 757
Gestation 757
Parturition 758
Lactation 759
Menopause 761
Growth, Maturity, Senescence and Death 761
Summary 763
Bibliography 767

ELEMENTS OF PHYSIOLOGY.

PART I.

THE NATURE AND CAPACITIES OF PROTOPLASM.

CHAPTER I.

THE PHYSICO-CHEMICAL ORGANIZATION OF PROTOPLASM.

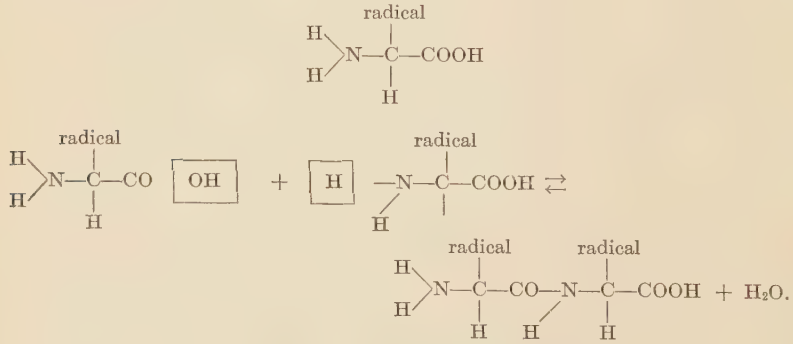
PROTOPLASM.

Protoplasm, the Seat of Life.—The task of physiology is to explain life as completely as possible, whatever its manifestations, and whether in plants, in animals, or in man himself. An overwhelming mass of evidence has convinced biologists that life as we know it on the earth is something that goes on only in, or in connection with, a particular kind of assemblage of materials, with certain fairly well-defined characteristics, to which is given the name *protoplasm*. Indeed, many physiologists are prepared to go further, and to hold that life actually is nothing more or less than the sum-total of such physical, physico-chemical and chemical activities as protoplasm displays. The holding of such a view has naturally led to the closest study of protoplasm, in the hope of gaining insight into the nature of the processes that make up what we call life. The study is very far indeed from being complete, but it has gone far enough so that we can venture some fairly definite statements about the organization and functioning of protoplasm, and can draw some interesting and suggestive inferences. These latter seem to be justified in the light of present knowledge. Some or all of them will have to be revised in respect to details as further data come to light.

Constituents of Protoplasm.—Protoplasm, as is well known, presents various appearances according to the sources from which it

is obtained. The details of its chemical composition are also exceedingly varied. There are, however, certain characteristics common to all or nearly all kinds of protoplasm; these will serve as the basis for a first description. The most abundant single constituent is water, more than 70 per cent of the mass of protoplasm usually consisting of this one substance. Dissolved in this water are many soluble substances. Some of these are simple inorganic salts, chiefly of sodium, potassium, calcium and magnesium, in combination as chlorides, phosphates or bicarbonates. Others are complex organic materials, like sugar, or soluble decomposition or derivation products of proteins. In addition to these dissolved materials there are present, also, certain other substances which are relatively insoluble in water. Chemically these belong chiefly either to the group of proteins or of phosphatides. They form 80 per cent or more of the non-watery part of protoplasm.

Proteins may be described as linkage products of amino-acids. The amino-acids that occur in Nature are compounds in which a "central" carbon atom is connected by one of its four valences to hydrogen, by another to a carboxyl group, COOH, by a third to an amino group, NH_2 (an imino group, NH, in the case of proline), and by the fourth to a radical of varying complexity, from simple hydrogen in glycine to a complex benzene ring-containing group in tryptophane (the attachment of the radical is not directly to the carbon atom in the two pyrrolidine-ring compounds, proline and oxyproline). The NH_2 group is on the opposite side of the C atom from the COOH group, as indicated in the diagram. When two amino-acids combine they do so by the union of the NH_2 group of one with the COOH group of the other, 1 molecule of water being eliminated as illustrated below:



This method of combination permits an almost indefinite linkage of amino-acids into ever larger and larger molecules. Hydrolysis of proteins by mineral acids or by digestive enzymes yields as many as 20 different amino-acids, at least 18 of which are probably

present in the proteins that enter into living protoplasm. The differences between one protein and another appear to depend on the relative amounts of the various amino-acids present, and on

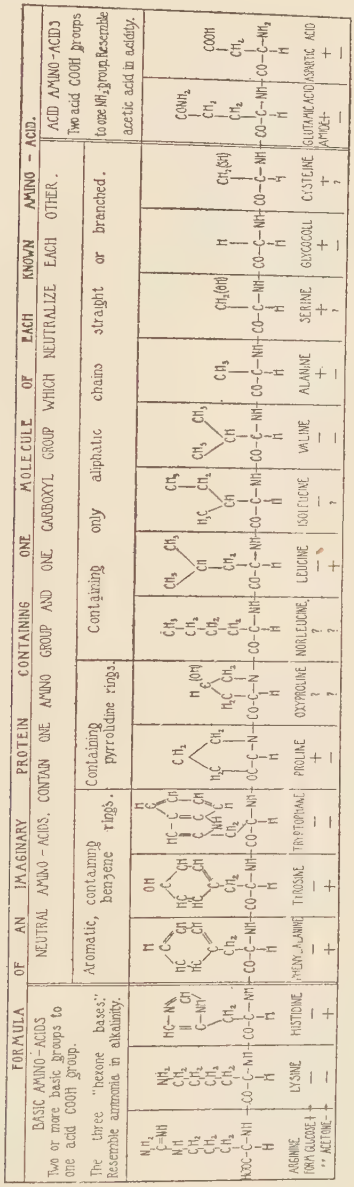
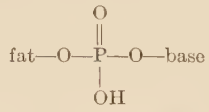


FIG. 1.—Formula of an imaginary protein containing 1 molecule of each amino-acid. (Van Slyke: Harvey Lectures, J. B. Lippincott Company, Publishers.)

the way in which they are arranged in the molecule. Abderhalden has calculated that the latter factor alone permits 2,432,902,008,176,640,000 different proteins to exist. The NH_2 groups, being allied to ammonia, tend to impart "basic" properties to the amino-acids; the COOH groups, on the other hand, tend to give the amino-acids "acidic" properties. Thirteen of the 18 amino-acids found commonly in proteins contain no amino or carboxyl groups other than the one of each in union with the "central" carbon atom (Fig. 1). In these the "basic" and "acidic" tendencies exactly neutralize each other (the amino group in the radical of tryptophane is so combined as to be ineffective). Three amino-acids, arginine, lysine and histidine, have amino groups in their radicals in addition to the one in union with the "central" carbon atom. These are accordingly predominantly "basic." Two others, glutamic acid and aspartic acid, have carboxyl groups in their radicals, making them predominantly "acidic." It is clear that the "basic" or "acidic" tendency of any protein, as a whole, depends on the proportion of these particular amino-acids in its molecules.

Phosphatides are fat-like constituents of protoplasm. Chemically a phosphatide molecule consists of phosphoric acid combined, on one hand, with a fat and, on the other, with an organic base.



In the best known of the phosphatides, lecithin, the base is an ammonia derivative, cholin. Lecithins may differ one from another in the character of the fats. The other known phosphatides, cephalin and sphyngomyelin, differ from lecithin and from each other in respect to the bases present, and also in other details that are as yet chiefly of chemical interest. Fat, as such, apparently does not enter into the composition of protoplasm. When present it is to be looked upon as a storage product. Only in union with phosphoric acid, as a phosphatide, can it play an active role.

There is a still less soluble group of substances, chemically alcohols, of which minute quantities are present in most kinds of cells. *Cholesterol* is the best-known example.

Physical and Chemical Forces Operate in Protoplasm.—In order to form any sort of picture of the organization of protoplasm it is necessary that we get some idea of how these relatively insoluble constituents, mainly proteins and phosphatides, are related to each other, as well as to the water of which protoplasm is chiefly composed, and to all the various materials dissolved in the water. The relationship is undoubtedly both physical and chemical. That is

to say, any physical or chemical forces that are in position to act will act and will tend to keep on acting until static equilibrium is reached. Since an essential feature of the life process is that static equilibrium is never attained during its continuance, we have in protoplasm a system that always tends toward the static condition, but in some way is prevented from reaching it while active life remains.

It is necessary here to draw a distinction between the state of being alive and the active life process. In many lower forms, as is well known, life is tided over from one season to another by a drying-out either of the whole body or of an offshoot from it (seed or spore). In this dried state static equilibrium is either attained or very closely approached. The prevailing view among those biologists that have investigated the subject directly seems to be one of doubt that theoretically complete static equilibrium can be reached short of death, yet in comparison with active life the condition in these dried forms is one of very great stability.

Protoplasm a Colloid.—There is abundant evidence to the effect that protoplasm has the particular physico-chemical organization known as the *colloid state*. This implies the presence in it of two or more *phases;* one phase is necessarily *continuous;* in ordinary protoplasm this phase consists of water with its dissolved constituents; the other phase (assuming but two for simplicity) is *discontinuous;* it consists of microscopic and ultramicroscopic aggregates, composed mainly, although as we shall see not wholly, of the relatively large and slightly soluble molecules of proteins, phosphatides, and possibly cholesterol. The existence of ultramicroscopic particles in protoplasm can be demonstrated by means of the ultramicroscope, a device which reflects light to the eye from objects too small to be brought within the range of vision by ordinary magnification with the compound microscope. An important feature of the ultramicroscopic particles in protoplasm is the presence in them of a considerable proportion of water (page 23). This fact places the protoplasmic colloids in the category of *emulsoids*, as distinct from suspensoids, in which the particles are solid.

MICELLÆ.

For reasons to be presented in later paragraphs it is believed that many of the most significant features of the life process are carried on in and by means of the ultramicroscopic aggregates just referred to. Various special designations have been suggested for them. Following the practice of Nägeli, Loeb, Michaelis and others, they are here called *micellæ* (plural of micella). Questions of great importance are what forces determine the grouping of molecules into aggregates, and particularly how such forces

determine the size of individual aggregates, keeping the majority of them at ultramicroscopic, *i. e.*, micellar dimensions. A force that must act is that of molecular attraction (known as *cohesion* when like molecules cling together, as *adhesion* when unlike molecules cling together). According to the conceptions of modern physical science, molecular attraction is a special manifestation of the same sort of force as causes chemical combinations to form, *i. e.*, electron stresses existing in some or all of the atoms of which the molecules are composed. In terms of this conception both cohesion of like molecules and adhesion of unlike imply a satisfaction of electronic stresses. In the particular case presented by the micellæ of protoplasm the molecules that cohere to form the basis of the aggregates are molecules of proteins or phosphatides (so little is known concerning the possible role of cholesterol that this substance is disregarded in this connection). Both these classes of substances have relatively huge and presumably highly irregular molecules; thus individual molecules present many superficial points where electronic stresses may prevail. A helpful conception (urged particularly by Loeb) is that some of these points of stress are so constituted as to be satisfied more readily by taking up (*adsorbing*) "polar" molecules, while others tend to attach to themselves "non-polar" molecules.

According to Langmuir, the distinction between a polar and a non-polar molecule is that in the former "the center of gravity of all electrons of the molecule does not coincide with that of the positive charges, so that the molecule acts as an electric dipole," while in the latter "the center of gravity of the electrons of the molecule (nearly) coincides with that of the positive charges of the nuclei, so that there is (little or) no dipole moment."

In general molecules of water, and of inorganic acids, bases and salts, are "polar," while large and complex organic molecules are "non-polar."

The effect of the presence of both "polar" and "non-polar" attractive points on the surfaces of individual protein and phosphatide molecules is to cause these molecules to tend to cling together by mutual attraction of their "non-polar" points, but less firmly than they would were all their attractive points of this type. Meanwhile in aggregates of large molecules thus formed there necessarily remain many unsatisfied points, because so constituted that the stresses are satisfied effectively only by adsorption of "polar" molecules. Protoplasm contains a great preponderance of molecules of the latter type, water and inorganic salts in the main. It follows of necessity that the protein and phosphatide molecules will tend to adsorb molecules of these substances. Thus in the formation of micellæ the large molecules will cling together, each tending to drag along with it its quota of "polar" molecules,

mainly water, since that substance is many times more abundant than any of the other "polar" compounds present.

Electrolytic Dissociation a Factor in Micellar Structure.—Although the attention thus far has been directed to the *molecules* which enter into the structure of micellæ, it is important to note that through electrolytic dissociation *ions* become involved as well, bringing into the picture various electrical stresses which must be considered in order to account for some of the most significant features of protoplasmic structure.

The fundamental fact of electrolytic dissociation is that when acids, bases or salts are in solution in water or other suitable solvent, a proportion of their molecules (determined by the concentration) dissociate into negatively charged *anions* and positively charged *cations*. In the undissociated molecules there is electrical neutrality. It follows that when dissociation occurs the positive charges borne by cations must exactly balance the negative charges borne by anions. The passage of a current through a solution of an electrolyte leads to a separation of ions, the cations migrating toward the cathode and the anions toward the anode. Water itself may become dissociated, but only to a very slight extent (page 24).

The fact has already been noted (page 20) that proteins may display acidic or basic properties. This implies that they may dissociate, since dissociation is a property of both acids and bases. The particular type of protein dissociation of interest here is one in which a superficial carboxyl group gives off a single positive hydrogen ion to form the cation, the remainder of the huge molecule becoming the anion, with a single negative charge.

Orientation of Anions in Micellar Surfaces. A significant conception in chemistry, as well as in physiology, is that of Langmuir and of Harkins, according to which importance attaches to the actual relations in space of molecules and ions to one another. Michaelis has applied this conception to micellar structure. He assumes that a proportion of the protein molecules are ionized as indicated above (the exact proportion depends on factors to be dealt with later; page 26), and furthermore, that the large anions are assembled at the surfaces of the micellæ, in such a position that the negatively charged carboxyl groups, from which hydrogen ions have separated off, are directed outward toward the water (the undissociated protein molecules are assumed to lie wholly within the micellæ, separated from the water by the intervening layer of definitely oriented anions). The effect of this arrangement is to give each micella as a whole a negative charge. Any positively charged ions, of hydrogen or other substances, that may be in the environment are attracted to the micellar surfaces, setting up a Helmholtz double layer about each. The electrical stresses thus established are thought to enter importantly as factors in the

life processes. They are brought up again in later paragraphs (page 28).

The Role of Inorganic Salts.—According to the picture presented in above paragraphs we might think of the inorganic salts as entering into micellar structure simply by becoming adsorbed on the polar points of the large molecules and ions in proportion to their respective concentrations in the protoplasm. In other words, the points of polar stress might conceivably be as completely satisfied by one kind of polar molecule or ion as another, in which case the only factor determining the partition of the various compounds would be their relative abundance. As a matter of fact, however, the inorganic salts have long been known to possess a significance in the organization of protoplasm out of proportion to their concentration therein. Indeed, the salts play roles of vital importance; we cannot imagine an organization of living substance from which they are absent. To understand something of why this is so it will be necessary to consider some physico-chemical facts bearing on the subject.

HYDROGEN-ION CONCENTRATION.

The relations of salts to proteins (and presumably to phosphatides as well) depend on the hydrogen-ion concentration of the system as a whole.

For a full presentation of hydrogen-ion concentration reference should be made to books devoted especially to the subject. A brief summary is given here in preparation for the discussions to follow, in which a grasp of the meaning of hydrogen-ion concentration is essential. Pure water undergoes electrolytic dissociation to a very slight extent. The hydrogen and OH′ ions, which are necessarily exactly equal in number, are present in concentrations of very nearly 10^{-7} times normal at ordinary temperatures. Under the law of mass action, for such very low concentrations as we are dealing with here, the product of the hydrogen ions by the OH′ ions is a constant. In this case the constant is $10^{-7} \times 10^{-7}$, or 10^{-14}. When hydrogen ions are introduced from the outside, as by adding an acid, the total number of hydrogen ions is increased, and so, since the product of hydrogen ions by OH′ ions is always constant, there is a reunion of OH′ ions with hydrogen ions to form water molecules until this constant product is regained, at which time there will be more hydrogen ions than OH′ ions left free in the solution. If OH′ ions are introduced, as by adding an alkali, exactly the reverse takes place. It should be noted that it is not the total quantity of acid or alkali that determines the resultant hydrogen-ion concentration, but the number of *dissociated hydrogen* or *hydroxyl ions*. Various acids differ in the extent to which they dissociate in equimolecular solution. The degree of dissociation determines

the effective strength of any acid. All degrees of acidity or alkalinity are expressed in terms of hydrogen-ion concentration. A solution is neutral only when the hydrogen-ion concentration is 10^{-7}, because that is the only concentration at which OH′ ions are also at 10^{-7}. Since we are using negative exponents the exponent becomes smaller the larger the number. In any solution that has a predominance of hydrogen ions the hydrogen-ion concentration will be expressed by 10 with a negative exponent less than 7. In a solution with a predominance of OH′ ions the hydrogen-ion concentration will be denoted by 10 with a negative exponent greater than 7. It was proposed by Sørensen, in 1909, that hydrogen-ion concentrations be expressed by using only the exponents with the negative signs omitted. The designation pH is employed to show that the Sørensen terminology is being used. This method of expression is very convenient in practice. One needs to remember that a pH of 7 stands for a neutral solution, that in acid solutions the pH values become smaller and smaller as the solutions become more and more acid down to a pH of 0, which stands for a solution normal in hydrogen ions, and that in alkaline solutions the pH values become larger and larger beyond 7 as the solutions become more alkaline, up to a pH of 14 for a solution normal in OH′ ions. The physiological range of hydrogen-ion concentrations is between about pH 5.5 on the acid side and pH 9.5 on the alkaline side.

Isoelectric Point.—In a former paragraph (page 20) the fact is pointed out that proteins may possess both "acidic" and "basic" properties on account of the presence in some of the constituent amino-acids of excess carboxyl groups and in others of excess amino groups. One must realize clearly, however, that the actual exhibition of either acidic or basic properties depends on the electrolytic dissociation of the protein molecules in such a way as to form either hydrogen or hydroxyl ions, or conceivably both at once. The dissociation of proteins is determined by the hydrogen-ion concentration in that there is for each one of them some critical pH value (known as the *isoelectric point*), at which hydrogen and hydroxyl ions are formed to equal extent, thus neutralizing each other. At higher hydrogen-ion concentrations (lower pH values) hydroxyl ions are in excess, the protein ion is positively charged and enters into chemical combination as a base. At hydrogen-ion concentrations below the isoelectric point (higher pH values) hydrogen ions are in excess and the protein ion has a negative charge, combining as an acid. (The fact that some proteins show an isoelectric *range* instead of a sharp isoelectric *point* does not vitiate the above conception.) The situation may be illustrated as follows: At its isoelectric point a protein will not combine with either acids nor bases to form salts. If by the addition of an acid the hydrogen-ion concentration is shifted away from the isoelectric point in the acid

direction the protein molecules begin to combine with the anions of the acid, the proportion of protein molecules entering combination becoming progressively greater as the hydrogen-ion concentration increases. If the acid used is HCl the compound formed will be protein chloride; if H_2SO_3, protein sulphate. Shifting the hydrogen-ion concentration away from the isoelectric point in the alkaline direction by the addition of a base causes the protein to enter combination with the basic cations, the proportion of protein molecules entering combination being again greater the farther away from the isoelectric point the hydrogen-ion concentration is carried. If the base is NaOH the salt formed will be sodium proteinate..

The discussion thus far has concerned itself only with proteins. Various investigators incline to the view that phosphatides display an analogous property. One should note that substances with this property are classed as *ampholites*.

Proteinates in Protoplasm.—The great importance of the above facts in physiology lies in the further fact that while the hydrogen-ion concentration of protoplasm is ordinarily somewhere near a pH value of 7.4, *i. e.*, slightly on the alkaline side of neutrality, the isoelectric points of some of the proteins present in it, if not all, are well on the acid side; pH values of 5 or less will probably include the isoelectric points of some of the most abundant of them. It follows that protoplasm contains both undissociated protein and protein in combination with the bases Na, K, Ca and Mg, forming proteinates, which are in turn dissociated into basic cations and proteinate anions. The proportion between combined and uncombined protein depends on how far away from pH 7.4 the isoelectric point of the protein in question happens to fall, since salt formation increases in proportion with the departure of the system from the isoelectric point.

Relation of Hydrogen-ion Concentration to the Structure of Micellæ.—According to the view of Michaelis (page 23), the surfaces of micellæ are composed of oriented anions. Consequently any agency which affects the proportion of anions is bound to affect micellar structure. We have just seen that hydrogen-ion concentration is such an agency. We may picture anions as coming to the surface or being displaced from the surface into the interior of the micellæ in the form of undissociated molecules with every shift in hydrogen-ion concentration. Furthermore, metallic salts being present, some of the anions on the surface will be in equilibrium with sodium, potassium, magnesium or calcium cations, while others may be present in equilibrium with hydrogen cations. Our picture of a micella, as thus far developed, indicates an ultramicroscopic "core," composed of undissociated molecules of proteins or phosphatides, or conceivably both, held together by cohesion of their non-polar points and accompanied by water and other polar molecules,

adsorbed at the polar points of the large molecules; surrounding this core is a surface layer of oriented proteinate or equivalent phosphatide anions, held by cohesion to like molecules beneath them. The orientation is such as to present the negatively charged points of the anions toward the outside, imparting to the micella as a whole a negative charge. Positively charged ions are attracted to this surface, establishing a Helmholtz double layer.

An additional suggestion, which may or may not be significant, is that the "polarity" of individual attractive points on the large molecules and ions may depend on the hydrogen-ion concentration. If this is so the firmness with which the micellar aggreatates hold together, and also the extent to which polar molecules are adsorbed into the micellæ, are altered with every change in hydrogen-ion concentration. Thus, the latter factor is seen to have possibly profound influence on fundamental micellar structure, and hence on the very basis of life itself.

DONNAN EQUILIBRIUM.

Donnan showed in 1911 that if two solutions of electrolytes, for example, $Na{\cdot}A'$ and $Na{\cdot}Cl'$, are separated by a membrane permeable to all the ions but one, the ions that can diffuse through will do so in such a proportion that when equilibrium is reached they will be found to be unequally distributed on the two sides of the membrane. Furthermore, the distribution will be such that the product of the number of diffusible cations and anions (of any given pair) will be the same on both sides of the membrane. Thus, if,

$$Na{\cdot}\ A' \ \mid \ Na{\cdot}\ Cl' \qquad \text{(initial state)}$$

in the example above, the membrane is permeable to cation $Na{\cdot}$ and to anion Cl', but impermeable to anion A', the only diffusible ions on the left side of the membrane at the beginning are cations $Na{\cdot}$, while on the right are cations $Na{\cdot}$ and anions Cl', both diffusible (see diagram marked "initial state"). Equilibrium is attained by a movement of both $Na{\cdot}$ and Cl' through the membrane toward A' until, as stated above, equal products of $Na{\cdot}$ and Cl' are reached on both sides. On account of the presence of a certain number of diffusible cations ($Na{\cdot}$) on the left to begin with, the products become equal before the electrolyte has become as concentrated on

$$\begin{matrix} Na{\cdot} & \left[\begin{matrix} \\ A' \end{matrix}\right] \\ + & \\ Na{\cdot} & \times\ Cl' \end{matrix} \ \Bigg| \ Na{\cdot} \times Cl' \qquad \text{(equilibrium state)}$$

the left as on the right (see diagram marked "equilibrium state"). It follows that in equilibrium there will be more diffusible cations

per unit of volume on the left than on the right, and more diffusible anions on the right than on the left; this situation is known as the "Donnan equilibrium."

To apply the principle of the Donnan equilibrium to protoplasm we have to note that a membrane is not essential to the unequal distribution of ions by which the equilibrium is established. What is necessary is that by some means one kind of ion be rendered indiffusible while the other kinds of ions present are left free to diffuse. In protoplasm the clinging together of proteinate or phosphatide ions in micellæ fulfils this condition. The aggregated ions are relatively fixed, while the associated metal cations are more or less free to migrate. A physical fact to be borne in mind is that micellæ, composed as are these, of large and complex molecules and ions of irregular shape and with many highly polar attractive points, can hardly be dense structures; they are rather to be thought of as networks, in whose interstices there is ample room for small molecules and ions to penetrate and move around. Furthermore, any molecules or ions that are held on or near the outer surface of a micella, as in the formation of a "double layer," form part of the micella itself, so far as the Donnan equilibrium is concerned.

Donnan Equilibrium in Relation to Protoplasm.—Loeb has advanced much evidence indicating that the Donnan equilibrium actually prevails in such micellæ as exist in protoplasm. As these micellæ were formed there must have been a migration into or upon them of some of the electrolytes dissolved in the water of the protoplasm, setting up the unequal distribution of ions characteristic of this equilibrium. Various important consequences are pointed out by Loeb; they include the setting up of electrical stresses and the establishment of differences of osmotic pressure between the micellæ and the surrounding medium. The theory of these effects need not be discussed here. It should be noted, however, that they are less pronounced in protoplasm, which contains inorganic salts, than they would be in a similar system containing only pure water and sufficient base to maintain the proteins at the hydrogen-ion concentration actually seen in protoplasm.

The electrical stresses presumably contribute to the maintenance of a negative charge on the micellæ. The fact that the micellæ are charged, and all negatively so far as present evidence indicates, is important for various reasons, only one of which is of concern at this point. In a former paragraph there is mention of the view that protoplasm, as a system in which the life process can occur, owes its capability in large part to the presence in it of micellæ of submicroscopic size. When we think of protein and phosphatide molecules and ions aggregating through molecular cohesion we will realize that if molecular attraction were the only force operating the aggregation would go right on, forming larger and larger masses,

until the substances precipitated out of the solution. As a matter of fact this is exactly what would tend to happen in both proteins and phosphatides at their isoelectric points, at which only molecules are present. At the hydrogen-ion concentration of protoplasm, however, at which both classes of substances are ionized to some extent, the micellæ that form through the mutual molecular attraction of protein and phosphatide molecules and ions are charged. All that are charged alike (which probably means all the micellæ) will tend to repel each other, and as soon as the intensity of this repulsion becomes as great as the force of molecular attraction the aggregation comes to an end. Under the conditions prevailing ordinarily in protoplasm this point is reached while many of the aggregates are still submicroscopic.

Discussion of the effects of the Donnan equilibrium on the osmotic relationships of protoplasm is deferred until the phenomenon of osmotic pressure itself has been considered (page 32). For other effects of the Donnan equilibrium (on viscosity and stability of solutions) the reader should consult Loeb or other authors who treat the topic.

SURFACE ENERGY.

There remains an additional consequence of molecular attraction as a force operative in determining the organization of protoplasm, to be described briefly before turning to the next phase of the topic.

In the micellæ as pictured the surface consists of anions so oriented as to present negatively charged groups (carboxyl groups when the micellæ are composed of proteins) to the exterior. It is obvious, however, that the configuration of the surface ions is not likely to be such that the only groupings exposed are carboxyls. Much more probably there are various non-polar attractive points at the surface, in addition to carboxyl and other polar points. To some extent the polar points, and to full extent the non-polar points, at the surface fail to have their attractive forces satisfied by mutual interaction with corresponding points on other molecules. Their surface position makes this inevitable. The result is the presence at the surface of each micella of a residue of unsatisfied electron stress, constituting a potential source of *free energy*.

To account for many known facts about the functioning of protoplasm some such intimate and immediately available source of energy seems necessary. Physiologists are accordingly disposed to lay great stress on *surface energy of micellæ* in explaining life processes. The reason why micellæ are more stressed than the larger microscopic aggregates that are also present is because surface energy becomes more effective the larger the surface in relation to the mass. It can be shown that in micellæ this relation is such as

to make possible the yielding of very significant amounts of energy. A fundamental fact of physics is that free energy always tends to become bound. In other words, a system containing free energy is never in static equilibrium, although always tending toward that state. There are at least two ways in which, in such a system as protoplasm, energy at the surfaces of micellæ can become bound. One is by the unsatisfied points attracting to themselves molecules dissolved in the water by which they are surrounded. The deposition of molecules on surfaces in this manner forms a case of what is known in physical chemistry as adsorption. The other is through the bending over and meeting of the lines of attraction on adjoining surface molecules (Mathews), thus setting up sidewise strains which form the basis of surface tension.

There is reason to believe that while in living protoplasm the micellæ tend to reach a state of stable equilibrium, through the satisfaction of their surface attraction in one or the other of these ways, they are actually prevented from coming into that state through the operation of other forces that will be described in Chapter III. In this prevention of static equilibrium the essence of the life process is thought to lie.

BROWNIAN MOVEMENT.

Molecular attraction is not the only physical force that influences the organization and the functioning of protoplasm. Protoplasm is predominantly liquid, and those of its molecules that are in the liquid state are in continuous motion in straight paths until collisions with other molecules or with micellæ or microscopic particles occur. Upon collision both particles rebound at angles determined by their angles of incidence. The result of the frequent collisions is that the actual paths, both of the molecules and of the suspended particles, are irregular zigzags. In suitably selected examples of living protoplasm microscopic particles in irregular motion can easily be seen. This motion has long been known; it is called *Brownian movement.* It is thought to be important in protoplasm by keeping the micellæ in motion, and so preventing them from clumping together.

OSMOTIC PRESSURE.

Another consequence of the motion of liquid molecules is probably of much greater significance. This is *osmotic pressure.*

Membranes can be selected or prepared that have various degrees of permeability to molecules. If we choose a membrane that will allow water molecules to pass but will hold back molecules of some dissolved substance, such as sugar (such a membrane is called semipermeable), and put on one side of this membrane pure water and

on the other side a solution of sugar in water, the situation, so far as the water is concerned, is virtually as though there were no membrane there at all, while the dissolved sugar is restrained from following its tendency to diffuse equally throughout the whole mass of water. In respect to diffusion dissolved substances were shown by Van't Hoff to behave in accordance with the laws of gas pressure. That is to say, the pressures they can exert in the course of their tendency to distribute themselves uniformly throughout solutions are precisely the same that the same quantities of substance would exert were they gases occupying a volume equal to that of the solution and under the same conditions of temperature.

When the diffusion of dissolved sugar is prevented by the interposition of a membrane impermeable to it its diffusion pressure, which may now be called osmotic pressure, comes into play in such a manner as to bring about as nearly as possible the same result that free diffusion would have, namely, an equal distribution of sugar through the water. Since the membrane prevents the sugar from moving into the water on the other side, the end is secured by a movement of the water through the membrane into the sugar solution. While the evidence is clear that osmotic pressure is really diffusion pressure of dissolved substances, there is as yet no satisfactory explanation of how this pressure operates to cause water to move, as it does, away from a region where this pressure is wanting or small into a region where it is present or greater. When we note that, if the membrane is made strong enough to carry the weight, columns of water 25 meters and more in height can be raised by osmotic pressure alone, the magnitude of the force becomes clear. Attempts to explain the phenomenon on the basis of unequal bombardment on the two sides of the membrane by water molecules, due to the obstruction offered on one side by dissolved substance, are not satisfactory because they transfer the driving force from the dissolved substance to the water, a transfer which introduces logical difficulties as great as those from which escape is sought.

In dealing with osmotic phenomena it is necessary to bear in mind that it is permissible to speak of the osmotic pressure of any solution, whether in relation to a membrane or not, and that osmotic pressure is stated in terms of the number of dissolved particles per unit of volume, irrespective of the nature of the particles. An exception to this statement applies in the case of *concentrated solutions*. (For details the reader should consult works referred to by Bayliss; see the end of the Chapter.) Osmotic pressure actually comes into play whenever two solutions of different osmotic pressure are separated by a membrane permeable to the solvent, and its magnitude is equal to the difference between the osmotic pressures of the two solutions. The movement of water, or other solvent, is always toward the more concentrated solution. The pressure is

exerted even when the membrane is permeable to the dissolved substances. Of course, when the membrane is thus permeable the dissolved substances will dialyze through (dialysis is diffusion through a membrane), and will presently equalize the osmotic pressure on the two sides, bringing movement of water to an end. Solutions of equal osmotic pressure are said to be *isotonic;* one of greater osmotic pressure than another is *hypertonic* with reference to it; of less osmotic pressure is *hypotonic.*

Relation of Osmotic Pressure to the Donnan Equilibrium.—Further discussion of the significance of osmotic pressure to protoplasm, and to vital processes in general will be found in Chapter XVI (page 250). At this point the effect of the Donnan equilibrium on the osmotic equilibrium between micellæ and the continuous watery phase of protoplasm calls for brief comment. It will be recalled than when the Donnan equilibrium exists the product of diffusible anions times diffusible cations inside and outside the micellæ is the same. To picture an extreme case let us suppose a micella has non-diffusible anions to the number of 30 per unit of volume, each with its corresponding diffusible cation; suppose also that when equilibrium is established the external medium has 8 molecules of completely dissociated monovalent salt per unit of volume. The product of diffusible anions times diffusible cations in the external medium is then 64 per unit volume; the same product must hold for the micellæ. Since we have postulated 30 diffusible cations in relation to non-diffusible anions equilibrium will be established when 2 molecules of completely dissociated monovalent salt per unit volume have migrated into the micellæ, giving altogether 32 diffusible cations and 2 diffusible anions, with the same product as above, *i. e.*, 64. But the total osmotic pressure of the external environment is that due to 16 ions per unit volume (the sum of anions and cations), while in the micellæ there are 34 diffusible ions per unit volume, indicating an osmotic pressure more than twice as great. It is clear that the Donnan equilibrium always has the effect of counteracting some osmotic pressure; in other words, the osmotic pressure within the micellæ cannot be the same as in the surrounding watery phase of the protoplasm. Furthermore, to the extent that the Donnan equilibrium obtains at the surfaces of separation of entire cells from their environment corresponding differences in osmotic pressure must exist between the cell contents and the surrounding tissue fluids. Further reference to this fact will be made later.

Chemical Activity Necessary to Life and Function.—Before concluding this account of the picture the data at hand have enabled us to form of the physico-chemical organization of protoplasm, we wish to emphasize the fact that the system, as described thus far, is one in which the free energy would not only *tend* to become bound,

but in which it would *actually succeed*. That is to say, under the operation of the purely physical forces that play a part in protoplasm the system would quickly settle into a state of relatively stable static equilibrium. This is to a considerable extent what happens in death. It follows that the life process, which acts to prevent this state of equilibrium from being reached, must include other forces than those yet mentioned. These forces are made available through chemical reactions. Their nature and role are the subject of Chapter III.

Summary.

Protoplasm, as a physico-chemical system, is pictured as an emulsoid, consisting of 70 per cent or more of water in which are dissolved various electrolytes and soluble non-electrolytes, and in which are suspended microscopic masses of various sorts, and vast numbers of submicroscopic particles, called micellæ. The microscopic masses and the micellæ consist chiefly of proteins and phosphatides, which at the hydrogen-ion concentration that prevails in protoplasm are present partly in molecular state and partly as metal proteinates and phosphatides. These latter compounds dissociate electrolytically into metal cations and complex anions. Under the force of molecular attraction the molecules and anions of proteins and phosphatides tend to cohere by their "non-polar" points into aggregates. In the formation of these aggregates water molecules and molecules of electrolytes are included in great numbers; in part by being dragged in through the attractive force of the "polar" points on the proteins and phosphatides; the electrolytes also because the fixation of the complex anions by coherence to one another fulfils the condition for the setting up of the Donnan equilibrium.

The micellæ are electrically charged; most of them, perhaps all, negatively. This is thought to be due in part to the orientation of the proteinate (and phosphatide) anions at the micellar surfaces in such position that the dissociated carboxyl or equivalent groups are directed outward, and in part to be a consequence of the Donnan equilibrium. An important effect of the existence of like charges on the micellæ is that they tend to repel each other, thus bringing into play a force which operates to restrict the size of most of the molecular aggregates in protoplasm to ultramicroscopic dimensions. A further influence perhaps tending to the same end is the Brownian movement, namely the keeping of the micellæ in irregular motion through their bombardment by the constantly moving liquid molecules.

Osmotic pressure is a force operative in protoplasm. One effect of the Donnan equilibrium is to maintain different osmotic pressures

within the micellæ than prevail in the continuous watery phase of the protoplasm; also, presumably, differences in osmotic pressure between the interior of cells and their liquid environment.

At the surfaces of the micellæ molecular stresses exist which are believed to form the basis for free surface energy; this, in turn, is thought to constitute the immediately available supply of energy for some types of protoplasmic functioning. Since in a system containing free energy there is always a tendency for the energy to become bound, a state of affairs inconsistent with the active life process, protoplasm must have some means of maintaining the micellar surfaces in their condition of available energy. This means is present in the form of chemical reactions.

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CHAPTER II.

CELL STRUCTURE AND THE CELL MEMBRANE.

CELL MEMBRANE.

Membranes Essential.—One of the cardinal facts of biology is that actively living substance, wherever it occurs, is incorporated into units, nearly always microscopic, called cells. Practically all kinds of cells show definite structural characteristics. Since, as was shown in the last chapter, protoplasm is predominantly liquid, the fact of cells, as well as of definite cell structure, argues that there must be some means by which the cell as a whole and its various parts are kept in place. Microscopic examination of a living protozoan with naked protoplasm, like amœba, reveals a sharp boundary surface between the living organism and the water in which it moves. One or more vacuoles, also with sharp boundary surfaces, can usually be seen. Under favorable conditions a clearly defined nucleus is visible. The only way in which we can explain these clear-cut surfaces between water and watery protoplasm, or between adjacent portions of protoplasm, is by assuming the presence of membranes. Furthermore, some of the things we know about the diverse chemical processes that can go on simultaneously within the confines of a single cell show that still other intracellular membranes, or structures that serve the purposes of membranes, must exist.

Membranes not only preserve the identity of the cell and of its parts, they also have a great deal to do with the carrying on of the life processes. These processes involve chemical reactions. Chemical reactions imply the presence of substances to react. The cell must receive these substances from outside itself. In entering they must penetrate the cell membrane. It follows that only such substances as are able to pass through cell membranes can have any share either in protoplasmic composition or in the chemical processes that are an essential part of life.

It is equally true that the composition of the cell membranes is determined by the substances present, either in the protoplasm or, in the case of the outer surface membrane, in the surrounding medium as well. Within the protoplasm we have proteins, phosphatides and cholesterol, and inorganic and organic soluble substances, including not only materials that have entered the cell through its membrane, but also a great variety of substances that are produced through the chemical activities going on in the cell. What the surrounding medium may contribute will depend on where

the cell lives. If it is a marine protozoan it is surrounded by sea water, which carries in solution every stable water-soluble substance that exists in Nature. If it is a cell of the human body it is surrounded by human tissue fluid (page 246), a medium of great complexity, in some respects similar to, and in other respects very different from sea water.

The cell boundary is a surface of demarcation between protoplasm and some dissimilar medium. (This statement does not hold strictly, of course, for multicellular forms, in which adjacent cells may be pressed closely together over much of their surface. The latter case corresponds with the situation inside the cell, where intracellular membranes occur, and will be considered in that connection.)

At any surface of contact of dissimilar liquids, or of a liquid with a gas, the molecular stresses characteristic of surfaces exist, and so such forces as surface tension may come into play. The fact has already been pointed out that free surface energy shares with all other manifestations of free energy the tendency to become bound. On page 30 it was stated that one way in which this may happen is by the condensation on the surface of substances which satisfy the surface stresses. This condensation, or *adsorption*, may be shared by substances both within and without the protoplasm.

Cell Membranes Are Equilibrium Membranes.—Only by study of its properties can it be determined whether the cell membrane is an adsorption membrane, and if so which of the many substances present within and without the protoplasm are included in the surface condensation, and in what proportions. This sort of study has been carried on extensively. A summary of the conclusions to which it has led, up to the present time, is all that can be presented here. The first item is that the membrane is an adsorption membrane, in the strict sense. This statement carries with it the important implication that the composition of the membrane is a matter of equilibrium among all the possible constituents present in the environment, both within and without the cell. The significance of the membrane as an equilibrium membrane is that the introduction of any new substances, or a change in the proportions of substances already present, by causing a shift in the equilibrium within the system as a whole, brings about a reorganization of the membrane to correspond. In protoplasm there is constant chemical activity, with consequent change in proportions of the substances present. It follows that the cell membrane is in constant process of remaking. It is probable, to be sure, that these effects are relatively slight, so far as they are due to the chemical activities that make up the ordinary life process. The really significant changes in membrane constitution result from alterations in the external environment.

Organization of Cell Membranes.—Cell membranes must be composed largely of the same materials as make up protoplasm. Accordingly we assume them to consist primarily of a compact layer of micellæ on which are adsorbed such molecules from within or without the cells as are most effective in reducing surface energy. Various lines of evidence indicate that in cell membranes micellæ composed of cholesterol and phosphatide (the least soluble protoplasmic constituents) predominate over protein micellæ, although the latter are by no means absent. The exact proportions in which adsorbed molecules occur are assumed to be determined in the main by the extent to which the different kinds are effective in satisfying surface electron stresses, but in part also by the relative concentrations of the various constituents in the system as a whole; this latter in accordance with the action of the "mass law" on an equilibrium structure.

We obtain thus a picture of a surface layer in which phosphatide, cholesterol and protein micellæ form a mosaic, of which the interstices are occupied more or less fully by molecules of water, of inorganic salts and perhaps of other substances, like urea, present in the system. The permeability of the membrane depends, presumably, in part on the number, size and shape of these interstices, in part on the character of the molecules (or ions) that occupy them, and in part on effects due to the existence of the Donnan equilibrium which the membrane sets up by permitting some ions to diffuse more freely than others. Since the membrane is an equilibrium membrane its permeability is not constant, but varies as the internal or external medium changes in composition.

Two lines of investigation have been particularly helpful in bringing out suggestions bearing on the nature of membrane permeability. These are: (1) Those on so-called "salt antagonism," and (2) those on the effects of narcotics of the chloroform-ether type.

MEMBRANE PERMEABILITY.

Salts and Membrane Permeability.—It has long been known that certain mixtures of inorganic salts are more favorable to cell survival than others. Ringer's solution, which consists of salts of sodium, calcium and potassium in virtually the same proportions as in sea water, but only about one-fourth as concentrated (NaCl, $\frac{M}{8}$; $CaCl_2$, $\frac{M}{400}$; KCl, $\frac{M}{200}$; enough $NaHCO_3$ to give a pH of about 8) was introduced in the eighties of the last century. Loeb suggested that salt antagonism might be a membrane phenomenon. Osterhout demonstrated this to be the fact by a series of studies of the electrical conductivities of tissues. Basing his method on the

justifiable assumption that the chief seat of electrical resistance in a tissue is in the membranes, Osterhout determined the effects of various salts on the conductivity of masses of the kelp, *Laminaria*. He showed that the fresh living tissue has a characteristic conductivity corresponding to a definite degree of permeability of the membranes to ions. Immersing the tissue in pure sodium chloride solution isotonic with sea water, increases the permeability; immersion in calcium chloride solution, also isotonic with sea water, decreases the permeability. A mixture of the two salts in approximately the proportion in which their cations occur in the ocean, namely, about 2 molecules of $CaCl_2$ to each 100 molecules of NaCl, maintains normal permeability.

Hildebrand and co-workers have recently suggested a means by which these facts may be used in forming a picture of the cell membrane, in relation to permeability. According to the theory of orientation of anions at the micellar surfaces (page 23) the points of attachment of the complex proteinate (or phosphatide) ions to Na and Ca are outward, each resulting molecule (neglecting dissociation for the moment) lying with its metallic constituent facing the watery phase, and its non-metallic portion beneath, within the micella. Monovalent Na is in combination with just one complex anion, while bivalent Ca unites with two. If we assume, as Hildebrand *et al.* propose, that the configuration of these molecules is such that the metallic portion occupies a larger cross-section than a single organic radical, but less than two such radicals, the Na-containing molecules may be pictured as wedges with their broad ends outward, and the Ca-containing molecules as wedges with their broad ends inward (Fig. 2). It follows that micellæ whose surfaces include only Na compounds will be approximately spherical, a form favorable to maximal size of interstices, and hence maximal permeability, while micellæ whose surfaces include Ca compounds will be elongated in proportion to the percentage of Ca-containing molecules (complete replacement of Na by Ca would imply a reversal of phase, water micellæ becoming inclosed in a matrix of proteins and phosphatides), decreasing the permeability to correspond. The difference is illustrated in Fig. 2. Normal permeability depends on a ratio of about 2 Ca-containing molecules to 100 Na-containing, indicating that the distortion of the micellæ in the normal cell membrane is relatively slight.

Narcotics Decrease Membrane Permeability.—That such narcotics as alcohol, ether and chloroform produce their effects primarily by decreasing the permeability of the cell membranes has been proved experimentally. The striking characteristic of these substances seeming to be significant in this connection is that they are solvents of phosphatides. That is to say, the molecules of phosphatides and of these substances have exceptionally strong attractive power

toward each other. It follows that in the presence of one of these narcotics each phosphatide molecule of the surface layer becomes surrounded by molecules of the narcotic. The effect of this would be to diminish in size or even close many of the interstices among the phosphatide molecules. It is true that not all phosphatide solvents are narcotics, nor are all narcotics phosphatide solvents. The narcotic action depends on decreasing the permeability of the cell membrane. It is conceivable that some materials may have strong attraction of phosphatide molecules and yet not attach themselves in such a way as to cut down the interstices seriously. The narcotic action of non-phosphatide solvents may easily be referred to other than the phosphatide constituents of the membrane.

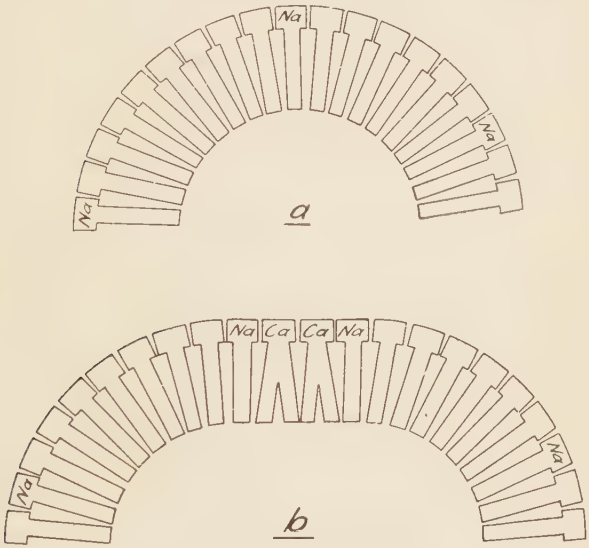

FIG. 2.—Diagram to suggest possible configurations of micellæ in cell membranes: *a*, When monovalent (Na) ions are the only metallic ions present; *b*, when some bivalent (Ca) ions are present as well.

A feature of the action of narcotics is that if the concentration of the narcotic in the environment is not permitted to become excessive the cell membrane may be held in its condition of lessened permeability for a considerable period of time. Furthermore, the action is reversible. That is to say, upon withdrawal of the narcotic from the cell environment the molecules of the narcotic substance are expelled from the cell membrane and the normal permeability is restored. Drug anesthesia is a practical procedure in human surgery because these two things are so. When present in excess the phosphatide-solvent narcotics are lethal. This fact is

explained by supposing that in high concentration the narcotics actually dissolve away some of the phosphatide portions, both of the cell membrane and of the underlying protoplasm, thus removing essential elements of the system.

In evaluating the above paragraphs the reader should keep in mind that the phenomena of salt antagonism, of narcotic action and of the electrical conductivity of tissues are experimental data, susceptible of verification at any time. The picture of cell-membrane organization that is presented is, on the other hand, a justifiable inference, based on the knowledge now at hand, helpful in interpreting cell functioning, but subject to revision as additional facts come to light.

CELL STRUCTURE.

Cell Walls.—In almost all plant cells, and in many kinds of animal cells, there is a separation out at the cell surfaces of relatively large quantities of substances wholly insoluble in water, giving rise to permanent, and usually rigid, cell walls. Whether these substances are organic, like the cellulose of plants and the chitin of arthropods, or inorganic, like the carbonates and silicates found enclosing many unicellular organisms, their appearance at the cell surface results from their previous production within the protoplasm, due to chemical activities going on therein. Although these materials are deposited at the cell surface, they do not constitute portions of the cell membrane proper. They play no part in regulating the intake or output of substances into or from the cell. They are freely permeable to all the kinds of molecules that enter into protoplasmic structure or functioning. The cell wall, as distinct from the cell membrane, plays a purely mechanical role, of support or protection against injury.

Intracellular Membranes.—Intracellular membranes and the surfaces of contact of adjacent cells present some difficulties of explanation from the physico-chemical standpoint, because instead of forming the boundary between quite dissimilar media they separate portions of the same medium. It is true, however, that there is adequate evidence showing that considerable chemical differences can and do exist between different portions of a single cell. We can best account for intracellular membranes by supposing them to be boundary surfaces between chemically dissimilar regions within the protoplasm. The best actual evidence we have for such chemical dissimilarity is furnished by the nuclear membrane, it being known that the nucleus consists largely of materials that are either absent from or very sparingly represented in the cytoplasm. Intracellular membranes are best explained as equilibrium membranes, just as are the membranes at the cell surfaces. They are accordingly subject to modification in character or position as the chemical activities

going on within the protoplasm change the equilibrium of the system as a whole.

The Nucleus.—Cell structure varies so widely in different kinds of cells as to make general statements of little value, except in the case of the nucleus. This latter is present as a definite and easily recognizable object in nearly all kinds of cells except bacteria. In the latter group, and in other forms in which definite nuclei are not demonstrable, nuclear material is believed to occur, but distributed throughout the cell mass instead of aggregated into a single structure.

Chemically, nuclear material is characterized by its high content of an exceedingly complex compound of nucleic acid with protein, called nucleoprotein. Nucleic acid is a union of four radicals known as nucleotides, each of which consists of a sugar group (hexose in animals) combined on one side with phosphoric acid and on the other with a purine base (a pyrimidine may also be present in plants).

Structurally, the nucleoproteins are assembled into definite units called chromosomes. The number of chromosomes is typically constant for all the cells of all animals or plants of a single species (maturated germ cells excepted). They are derived from the fertilized egg by a process of such a sort that the chromosome content of each cell of any individual is an exact duplicate of that in any other cell in the same individual. The evidence furnished by genetics shows, further, that each chromosome is an aggregate of still smaller units, known as genes. These latter, in all the forms that have been studied, are arranged in definite linear order. Whether the genes are single molecules or micellæ is not known. The remarkable part they play in heredity suggests the latter. They must be chemical or physico-chemical units of a high degree of stability, although, as the phenomenon of mutation shows, not wholly insusceptible of change. The genes exercise control, both in general and in particular, over the whole process of development, subject to such influences as the environment may bring to bear. The nature of this control, whose explanation is a phase of cell physiology, is at present wholly unknown. No speculation regarding it is in order except as one may suggest that the genes probably constitute an equilibrium system, both among themselves and with the protoplasmic mass of the cell as a whole. (For further discussion of the relation of the genes to heredity the reader is referred to works dealing especially with the subject.)

Nuclear Function.—The function of the nucleus, and by implication of the chromosomes, is by no means confined to the period of cell multiplication and cell development. There is abundant evidence that the normal life process involves chemical activity of the nucleus and cytoplasm in interrelation. During the "resting stage" the nucleus no longer presents the appearance of discrete chromo-

somes in definite numbers. The chromatin material is more or less completely fused into networks or irregular masses, although it is known that the identity of the chromosomes is not lost. The space within the nuclear membrane is not wholly occupied by chromatin. In fact only a relatively small fraction of it is so occupied. The entire contents are referred to as *karyoplasm*, to distinguish them from the protoplasmic material outside the nuclear membrane, which constitutes the *cytoplasm* (Fig. 3). That the karyoplasm is a micellar system surrounding the chromatin network, and differing

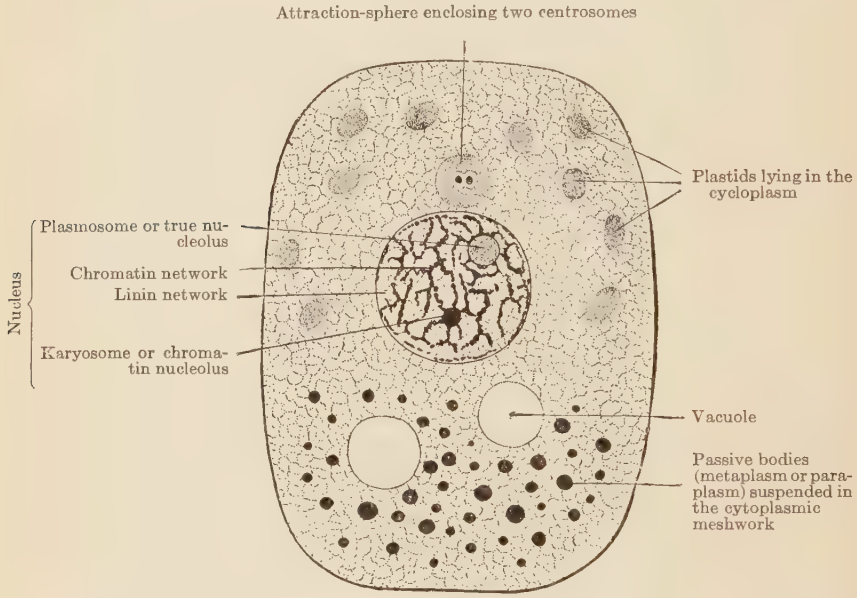

FIG. 3.—Diagram of a cell (Wilson). The non-homogeneous character of the cytoplasm and karyoplasm is indicated by the meshwork background. Specialized portions of cytoplasm (plastids) having definite functions are also shown. (Starling's Physiology.)

chemically from the cytoplasmic micellar system, is evidenced chiefly by the existence of the nuclear membrane itself. The fact that in most kinds of cells, at a certain early stage in cell multiplication, the nuclear membrane disappears, suggests that, with the separation of the chromosomes as definite structures, such chemical differences as had previously existed between karyoplasm and cytoplasm are equalized, and so the necessary physico-chemical conditions for the maintenance of a membrane are lost.

It has been found possible, by a process of microdissection, to obtain living protozoa from which all nuclear material has been

removed. Organisms so treated may live for several days. It appears, however, that all chemical activities shown in such preparations are at the expense of materials that were within the cytoplasm in available form at the time the nucleus was removed. The power of taking in and utilizing fresh supplies (except of oxygen) from outside seems to be completely lost. This shows the nucleus to be particularly concerned with that part of the life process in which the various kinds of materials that enter the cell are worked over into the forms they must have if they are to be of use to the cell. There is evidence, also, that the process of growth, a process that involves a special series of chemical reactions, as will be seen in a later chapter, cannot go on except in cells containing nuclei.

Special Cytoplasmic Structures.—Many kinds of cells, after suitable staining, show particles barely above the lower limit of microscopic vision, known as *mitochondria*. These particles have been shown to be composed mainly of phosphatides. The suggestion has been made that their surfaces are the seats of certain of the chemical syntheses of which protoplasm is capable, as of protein from amino-acids (page 53).

Plant cells usually contain easily demonstrable structures known as *plastids* which are obviously subdivisions of cytoplasm set off by intracellular membranes to subserve special functions. Thus, the chlorophyll (page 52) is confined to definite *chloroplasts;* other plastids are thought to be concerned in the conversion of sugar to starch.

The specialized cells of higher animals, muscle, nerve and gland cells show definite cytoplasmic structure associated with their special functions. Reference will be made to the most important of these when the tissues containing them are under discussion.

Summary.

Protoplasm is organized into units, called cells. The boundary surface of the cell is presumed to be a micellar condensation, composing the cell membrane. There is evidence for the existence of intracellular membranes as well, by which different parts of the cell are set off from one another. The nuclear membrane is the best-known example.

The existence of the cell membrane is thought to depend on the fact that the cell surface is a boundary between dissimilar media. Molecules from within and without the cell are adsorbed on the membrane in proportion as they tend to reduce free surface energy or in accordance with the Donnan equilibrium. The mass law operates also as a factor, with the effect that the cell membrane is

essentially an equilibrium membrane, varying in detailed composition with all changes either within or immediately without the cell.

Evidence obtained largely from studies of the electrical conductivity of tissues, of "salt antagonism," and of the effects of narcotics, leads to the inference that the cell membrane is composed basically of a layer of closely packed micellæ, phosphatide and cholesterol micellæ predominating over protein micellæ. The micellæ are pictured as forming a mosaic, the permeability of which depends in part on the number, size and shape of the interstices among the micellæ, in part on the extent to which adsorbed molecules occlude the interstices, and in part on the effect of the Donnan equilibrium, which is necessarily a factor since the membrane permits more ready diffusion of some ions than of others.

No substances can enter into the composition of protoplasm, nor share in the chemical activities that make up the life processes, except such as are able to penetrate the cell membrane.

Cell walls, as distinct from cell membranes, represent the deposition at the cell surface of insoluble products of cellular activity, presumably in accordance with the same forces as cause the formation of the cell membrane proper. Cell walls function mechanically, as support or for protection against injury; they play no part in regulating membrane permeability.

Intracellular membranes and the surfaces of contact of adjacent cells represent protoplasmic condensations at boundaries between chemically dissimilar areas within the mass of protoplasm. This conclusion is based on two points: (1) That chemical dissimilarities are known to exist within the boundaries of single cells; (2) that the physico-chemical conditions for membrane formation are not known to be fulfilled except at surfaces between dissimilar media.

A constant structural feature of cells is the nucleus. The chief special constituent of nuclei is nucleoprotein. This substance makes up the major portion of the chromosomes, which are definite units, typically constant in number in the cells of all plants or animals of a single species, and derived from the fertilized egg by a process of such a sort that the chromosome content of each cell of any individual is an exact duplicate of that in any other cell in the same individual.

The nucleus is the carrier of hereditary traits. It also controls development, subject to the influence of environment. Cell growth depends on the nucleus. Those phases of the life process which involve the working over of raw materials into utilizable form also depend on the nucleus, since they fail to go on in cells that have been deprived of their nuclei, although such cells may live for a time on the supply of utilizable material that was present when the nucleus was removed.

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CHAPTER III.

METABOLISM: THE CHEMISTRY OF THE LIFE PROCESSES.

METABOLISM.

Metabolism Defined.—There has been repeated reference to the fact that protoplasm is the seat of continuous chemical activity. For convenience in designating those chemical processes that go on in living protoplasm the term *metabolism* has been adopted. This is a word of general meaning, intended to cover the sum total of the chemical activities of living things, whatever their character, or whatever their effects.

The Term Covers Very Many Reactions.—The almost inconceivable richness and variety of the metabolic processes can scarcely be overstressed. To appreciate something of the versatility of protoplasm as a chemical laboratory and workshop one has but to recall that the number of distinct species of living things on the earth undoubtedly runs into the millions, and that the differences between species must be at bottom chemical differences, and further, that in any single complex animal or plant a great many different substances are reacting and interacting in most complex fashion. Thousands of organic compounds, many of them of the very highest usefulness to mankind, are synthesized automatically, some of them apparently incidentally, as a feature of the metabolism of animals and plants. The chemist is now able to obtain many of these same substances in his laboratory through series of controlled chemical reactions, but still a large proportion of the processes of which protoplasm is capable, including what is frequently described as "the most important reaction in Nature," namely, the synthesis of sugar from carbon dioxide and water in chlorophyll-containing plant cells, defy his efforts.

Any account of metabolism must necessarily be restricted to a comparatively small proportion of the substances that enter, and must deal with reactions in general terms, since the details of protoplasmic chemistry are as yet very imperfectly known. As we have already seen, every living cell is a unit of the protoplasmic workshop and laboratory. The reacting substances are either in solution in the watery phase of the emulsoid or are included within the micellæ or the microscopic particles. A point that should be stressed (Loeb) is that the large proportion of water in the submicroscopic micellæ favors the occurrence of chemical processes within them.

The same would apply to the microscopic particles, or at least to such of them as are actually part of the living structure and not masses of precipitated substance.

Reactions Classified.—The chemical reactions that occur in protoplasm may be classified as follows: (*a*) Simple adjustments for the restoration of equilibrium, with little or no energy involvement; an example of this type is presented in connection with the evolution of carbon dioxide in cells; CO_2 is produced more or less continuously as the result of reactions of another class, to be described presently; the setting free of this acid substance in a system containing basic salts (the hydrogen-ion concentration of protoplasm is on the alkaline side of neutrality) results in the familiar reactions tending toward neutralization. (*b*) Decomposition of complex compounds into simpler, and synthesis of complex compounds from simpler without much energy involvement; reactions of this class are readily reversible; examples are the hydrolysis of proteins into amino-acids, and the synthesis of proteins from amino-acids; to be included under this head are reactions between complex substances with the formation of other complex substances, again without much energy involvement. (*c*) Decomposition of complex compounds of high energy value into simpler compounds of less energy value, with liberation of energy. Reactions of this type are exothermal; they are believed to be of great importance in connection with some functions of protoplasm, particularly in muscular contraction. (*d*) Synthesis of complex compounds of high energy value from simpler compounds of less energy value; reactions of this type are endothermal; the best example, although because of its involvement of an outside energy source not admitted by all physiologists to the category of metabolism, is the synthesis of sugar from carbon dioxide and water, already referred to; this reaction, known as *photosynthesis*, by which the energy of sunlight is transformed into potential chemical energy, lies at the basis of most vital manifestations (the so-called autotrophic bacteria appear to be completely independent of photosynthesis); in photosynthesis oxygen is set free (other endothermal syntheses occur in Nature of which oxygen surplus is not a feature). (*e*) Exothermal combinations of the sort typified by *oxidation*.

Animal Metabolism Exothermal.—On the whole, metabolism in animals is exothermal; the same is true of saprophytic plants, but the reverse holds for green plants on account of the predominance of photosynthesis in them. Many endothermal reactions occur in animals, but the energy necessary for their accomplishment must be provided in all cases by concurrent or approximately concurrent exothermal reactions. The chemical basis for all these traces back ultimately to products of photosynthesis; hence the energy traces back to the sunlight.

BIOLOGICAL OXIDATION.

Oxidation.—Sugar is the basic energy-providing substance in Nature; it is to be expected, therefore, that reactions in which sugar or sugar derivatives are decomposed will play a large part in animal metabolism. In the endothermal synthesis of sugar oxygen is set free; in its exothermal decomposition oxygen is absorbed. The source of the oxygen is the atmosphere. The process of combination is known as *biological oxidation.*

Oxidations in general received their name originally because as first studied they appeared to include only reactions in which oxygen enters into combination. Modern chemistry extends the term oxidation to include all reactions in which there is a transfer of electrons from the substance "oxidized," known as the *reductant,* to the substance "reduced," known as the *oxidant.* In other words, oxidation is strictly *deëlectronation* and reduction *electronation.*

To emphasize the fact that in an electron shift both a donor and a recipient of electrons are concerned, the practice has been adopted of describing the reactions as *oxidation-reduction* reactions. The tendency of electrons to shift from reductant to oxidant in any given oxidation-reduction system depends on the *electron instability* ("electron fugacity," according to Needham and Needham), and as shown by Clark is measured by the *reduction potential* of the system (many authors prefer the term oxidation-reduction potential).

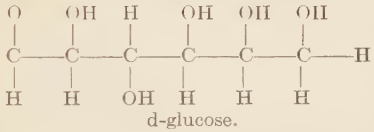
The majority of chemical reactions (oxidation-reduction reactions among the number) proceed with measurable velocity. This fact implies that at any given instant only part of the molecules present are reacting. To account for this the conception of "active molecules" has been advanced. An "active" molecule is presumed to be one in which certain electron pairs have come in the course of their orbital motion into positions of instability. The percentage of molecules becoming active per unit of time is a function of the temperature, a fact which finds expression in the familiar "positive temperature coefficient."

Under certain conditions the electrons whose shifts underly the reactions displayed by a given system assume positions of greater instability than usual. Molecules in which this has occurred are said to be "activated." In an oxidation-reduction system activated molecules will have a higher reduction potential than inactivated.

Hexose sugar is the reductant most extensively involved in biological oxidations. Under ordinary conditions the reduction potentials between this substance and atmospheric oxygen are too low for oxidation-reduction to take place. Yet one of the most familiar facts of physiology is that atmospheric oxygen serves as ultimate oxidant in the oxidations occurring in the animal body. Evidently

some sort of "activation" either of sugar molecules or oxygen molecules, or both, takes place. According to the theory of Wieland, which at present is commanding particular attention, the activation of prime importance is of the sugar molecules, and is confined, in fact, to the hydrogen atoms thereof. In other words, the electron pairs brought into positions of exceptional instability are associated with hydrogen atoms. The agencies by which activation is accomplished appear to be enzymes (page 53), present in ample quantity in practically all living cells.

Hydrogen Transport a Factor.—Much evidence has accumulated showing that in most, if not all, biological oxidations the underlying electron shift is mediated by an actual transfer of hydrogen from reductant to oxidant, the reductant suffering dehydrogenation and the oxidant becoming hydrogenated. As applied to the oxidation of sugar this would imply steps somewhat as follows (disregarding intermediary compounds which are known to be formed): The sugar itself disappears along with molecular oxygen, while CO_2 and H_2O_2 (subsequently to be decomposed into water and molecular oxygen) are produced. The linkages binding carbon to hydrogen or hydroxyl (see structural formula), and also those binding carbon to carbon, are all replaced by linkages with oxygen. A salient con-



d-glucose.

ception of the Wieland theory is that the oxygen thus taken up is not molecular, but is derived from the surrounding ionized water. The utilization of oxygen from this source, however, necessarily leaves hydrogen from the same source in surplus. Part of this surplus hydrogen is presumed to form water by union with OH radicals from the sugar; the remainder to join with the hydrogen undergoing transport from sugar as reductant to oxygen as oxidant, with formation of H_2O_2.

Hydrogen Transporters.—It is doubtful whether the transport of hydrogen from sugar or other fuel stuff to oxygen is ever direct in the animal body; an intermediary stage appears always to be involved. That is, the hydrogen passes over from the fuel molecule to some "hydrogen acceptor" present as a constant constituent of the cells, and is "donated" in turn by this substance to molecular oxygen (in anaërobic forms some other final hydrogen acceptor functions in place of oxygen; next page). The intermediary substance thus performs the role of "hydrogen transporter." Its salient characteristic is that it acts alternately as acceptor and donator of hydrogen. In plant tissues polyphenols appear to act

as hydrogen transporters; in animal tissues two or more quite different types of compound are recognized as functioning in the same capacity.

Glutathione.—An important advance in our knowledge of oxidations in animal tissues was secured when Hopkins isolated from tissues a thiol compound, to which he assigned the name *glutathione*, which functions as hydrogen transporter. The substance is a dipeptide of cystein and glutamic acid. The only feature of its complex molecular structure that concerns us here is the thiol (SH) group. For simplicity the molecule is indicated by the symbol GSH (following the practice of Hopkins). At the hydrogen-ion concentration usually prevailing in animal tissues (about pH 7.4), and provided a trace of iron is present (see below), the SH group tends to combine actively with molecular oxygen, forming a disulphide and H_2O_2, according to the following equation:

$$2GSH + O_2 = GS-SG + H_2O_2.$$

The disulphide at the same hydrogen-ion concentration tends to combine with "active" hydrogen, restoring the former state, as follows:

$$GS-SG + 2H = 2GSH.$$

Both reactions proceed simultaneously in tissues, thus catalyzing the oxidation of such reductants (hydrogen donators) as contain "active" hydrogen atoms.

Thyroxin.—Another substance, long known to be of prime importance in metabolism, but only recently thought of as functioning as a hydrogen transporter, is the hormone of the thyroid gland, lately isolated in the pure state by Kendall, and named by him *thyroxin*. The chemistry of the substance has been established only recently (page 198); consequently information as to how it performs its function as hydrogen transporter (provided it proves on further investigation to have that function) remains to be obtained.

It is altogether likely that other hydrogen transporters occur in the body. Further study will probably bring them to light.

Anaërobic Metabolism.—There are certain organisms whose metabolism dispenses altogether with free oxygen. These are known as *anaërobes*. Others do without free oxygen under some conditions and use it, or may even require it, under different conditions; these are *facultative anaërobes*. Anaërobic metabolism implies in these organisms the operation of some other final hydrogen acceptor than molecular oxygen.

Most mammalian tissues can display a type of anaërobic metabolism, brought into evidence whenever sufficient oxygen supplies fail to be provided (page 91). The salient feature of this metab-

olism appears to be that oxidation-reduction processes drop out. At any rate, the chief indication that any tissue is suffering oxygen-want is the appearance of degradation-products of primary fuels, mainly lactic acid (page 91), among the products of its metabolism. So far as can be judged these degradation products are formed prior to actual oxidation-reduction, and their appearance is interpreted as signifying the absence of the latter type of reaction. Mammalian tissues are not, then, capable of anaërobic metabolism in the sense in which true anaërobes are.

The Activation of Oxygen.—The necessity that hydrogen atoms of a reductant be "activated" in order to establish an effective reduction potential between it and the hydrogen acceptors in tissues has already been pointed out (page 49). A view of physiological oxidation urged particularly by Warburg conceives the final stage of the process, *i. e.*, the union with oxygen itself, to require *oxygen* to be "activated" also. The activating agency, according to the observations of Warburg, is iron in certain special combinations. The fact that probably all cells contain iron in traces is in line with this conception, as is also the observation cited above (page 50) that the union of glutathione with oxygen requires the presence of iron.

Tissue oxidations are very effectively suppressed by cyanides; this is, in fact, the chief if not the only factor in the poisonous action of these compounds. In the view of Warburg the suppression is due to immobilization of the iron by causing it to enter into some form of inert combination with the cyanide.

Activation of oxygen is obviously not a factor in hydrogen transport in anaërobic organisms. Just how extensively it is involved in ordinary aërobic metabolism cannot be stated at present; it appears highly probable however that tissues have more or less power to complete the transport of hydrogen to molecular oxygen even when the latter has not been "activated."

Peroxidase and Catalase.—Hydrogen peroxide (H_2O_2) is produced whenever hydrogen is "accepted" by molecular oxygen in the course of such a biological oxidation as described above. The further fate of this compound appears to depend on which of two catalytic agencies, both widely present in tissues, dominates the situation. If the effective agent is *peroxidase* the H_2O_2 apparently itself undergoes "activation," with the result that secondary oxidations, involving other reductants than those concerned in the primary oxidation process, also occur (see Hopkins for details). These oxidations may be thought of as contributing to the complexity of tissue metabolism (page 46). They have the effect of removing the extra oxygen atoms from the peroxide molecules, leaving water as residue.

If *catalase* is the effective agent the peroxide is decomposed into water and molecular oxygen without activation, and consequently

without inducing secondary oxidations. Since one or the other of these catalyzers is always active, hydrogen peroxide is prevented from accumulating in the tissues; the presumption being that such an accumulation is injurious. The conditions determining which catalyzer shall be effective at any given moment are not yet known; they are presumably very significant factors in regulating metabolism.

The Substances Oxidized. The body burns hexose sugar chiefly (page 176), but immediate derivation products, like lactic acid, may also be oxidized (page 88). Much evidence is accumulating (to be considered later) that fats (page 185) and non-nitrogenous amino-acid residues (page 182), both known to be utilized as fuel in the body, are converted to carbohydrate before entering upon the energy-yielding reactions of oxidation. Carbohydrate molecules are exceedingly complex, and appear to undergo several or many partial decompositions with much rearrangement of atoms, in the linked reaction series in which their oxidations occur.

Space has been devoted to the biological oxidations because of their prime importance as the immediate means by which the potential energy contained in sugar and the sugar derivatives is made available for living protoplasm. Brief statements must be made also regarding the other types of reactions seen in metabolism.

Photosynthesis.—Photosynthesis will be outlined only for the sake of completeness, as this type of reaction has no precise counterpart in the higher animals. The necessary conditions are suitable temperature, adequate supplies of water and carbon dioxide, living cells containing structures known as chloroplasts, in which chlorophyll is the essential chemical constituent, and sunlight. The chemistry of chlorophyll is complex. As a matter of fact the term covers as many as four distinct compounds. There are two proper chlorophylls and two pigments associated in the system. The chlorophylls contain magnesium, as an interesting component. How the chloroplasts achieve the synthesis of sugar is not known. Chlorophyll is not a catalyst, and the action is not, at least primarily, an enzyme action. Formaldehyde appears in all experimental efforts to duplicate chlorophyll action in the laboratory, but it is by no means certain as yet that formaldehyde is an intermediate product of sugar synthesis as carried out in the green plant. Calculations show that of the total energy of light falling upon the chloroplasts about 20 per cent under ordinary conditions, and 40 per cent under very favorable conditions, may be converted into the potential energy of sugar (Bayliss).

Hydrolysis and Dehydration Synethesis.—Reactions of class *b*, in which not much energy is involved, are believed to belong invariably, or at least practically always, either to the general type of reaction known as *hydrolysis*, when decomposition of complex mole-

cules is occurring; or to the reverse reaction, *dehydration synthesis*, when simpler molecules are combining into more complex.

In hydrolysis water enters into combination as the first stage of the reaction; the taking up of water is followed by a splitting of the resultant molecule in such a manner as to leave a single hydrogen in union with one of the split-product molecules and a hydroxyl radical in union with the other. In the synthesis which is the reverse of hydrolysis a molecule of water is eliminated with each molecular union, one of the uniting molecules contributing hydrogen and the other hydroxyl. Hydrolysis, as well as the reverse synthesis, may occur in successive stages. Thus the exceedingly complex molecule of protein may be gradually broken up into its constituent amino-acids, or the amino-acids may be gradually built up into protein.

An important feature of these reactions is that when all the substances concerned, both initial and final, are soluble in water, hydrolysis is always attended by synthesis and synthesis by hydrolysis. As complex molecules begin to hydrolyze into simpler there is a continuous decrease in the number of the complex molecules present and a corresponding increase in the number of simpler. Under the law of mass action this leads to a resynthesis of complex molecules from simpler. Both reactions go on steadily and there must, of necessity, be some point where synthesis will exactly balance hydrolysis. This is the equilibrium point of the reactions. Note that this is not an equilibrium at which chemical activity ceases, but one at which two reactions balance one another. It is dynamic, not static. Where the quantity of water present is large, as in protoplasm, the equilibrium point is usually in the region of nearly complete hydrolysis; but in order for hydrolysis to be absolutely complete one or more of the products must be removed in some manner. If one is insoluble this end is secured; or immediate utilization in some other reaction gives the same result. Synthesis can, in like manner, be extensive only when some of its products are withdrawn.

ENZYMES.

The reactions of hydrolysis and of dehydration-synthesis would go on spontaneously only very slowly, under the conditions prevailing in protoplasm. They are made rapid enough to be serviceable in metabolism, without any change in final equilibrium, through the catalyzing action of *enzymes*. These agents are always present as constituents of protoplasm, as well as in various fluids elaborated by gland cells. They are supposed to be proteins, although they have not yet been obtained in pure state, and so their precise chemical nature remains uncertain. Through the

application of the principles of the Donnan equilibrium (page 27) to solutions of enzymes as fully purified as possible, Northrop and others have shown such as have been examined to behave like monovalent ions. In such a system as protoplasm the presence of ions of the relative magnitude of protein ions virtually implies the establishment of the Donnan equilibrium, and raises the presumption that the enzyme ions are aggregated into micellæ. Further evidence leading to the same conclusion is that mechanical disturbance, such as vigorous shaking, frequently abolishes enzyme action in solutions that have previously shown it markedly. It is known, also, that enzyme action is in large measure a surface effect.

The conclusion some investigators have drawn from these facts is that enzyme action may be in part, at least, due to the physicochemical nature of the enzymes, and not wholly to their chemical composition. An interesting further fact, reinforcing this idea, is that if enzyme-containing fluids are separated from pure water by a membrane permeable to small molecules, but not to large, dialysis robs the solution in course of time of its enzyme property, without the water outside the membrane acquiring it. The inference is that the escape of some small diffusible molecules or ions has destroyed the enzyme action. Proof that this inference is correct is furnished by the fact that the enzyme action is restored by replacing the material lost by dialysis with a suitable electrolyte. The simplest explanation seems to be that the enzyme property resides in micellæ of characteristic organization, and showing, of necessity, the Donnan equilibrium.

Enzymes are characterized by their effectiveness in small quantity; by the fact that they do not enter chemically into the reactions they catalyze, although they are so unstable that they usually decrease in quantity as the catalysis proceeds; by their susceptibility to small changes in hydrogen-ion concentration; by the so-called specificity of action, which is a restriction of the catalyzing power of any individual enzyme to substances of similar chemical composition, the restriction going so far as the arrangement of atoms within the molecules (if one member of a pair of optical isomers is catalyzed the other member is also, but at a much slower rate); by the way in which changes in temperature affect them. The rate of catalysis is proportional, up to a certain point, to the quantity of enzyme acting. Rise in temperature quickens catalysis, in accordance with the temperature coefficient of chemical processes generally, but also renders the enzyme less stable, so that it breaks down more and more rapidly as the temperature rises. It follows that the rate of catalysis will rise with the temperature until a point is reached, called the optimum, above which the breakdown of the enzyme outweighs the acceleration due to heat, and so the

catalysis becomes less rapid. It is an interesting fact that the optimum temperature for most enzymes is nearly the normal temperature of warm-blooded animals. Enzymes are completely destroyed by exposure to temperatures of 60° to 80° C. for one-half hour or more, or by brief boiling.

VITAMINS AND HORMONES.

Vitamins and Hormones as Factors in Metabolism.—Enzymes affect metabolism by quickening the various reactions that go on in protoplasm to a serviceable rate, without changing the final equilibria. There is evidence of at least two additional groups or classes of substances occurring in protoplasm and influencing metabolism. The mode of action of these is obscure. It is undoubtedly different for different members of the two classes. Disturbances of metabolism result from the absence of these substances from the cells, and also, in the case of some of them, from their presence in undue amounts. The members of one of these groups are called *vitamins;* of the other, *hormones*. Both classes of substances are discussed in some detail in later chapters (pages 193 and 197). At this point it is sufficient to note that they appear to be as essential to normal metabolism as are the better known enzymes. All the members of both these classes are extraordinarily potent in low concentration. Some of the hormones have been identified chemically, and for these it has been shown that they influence metabolism when in such dilution that the protoplasm cannot possibly contain more than one molecule of the hormone to several million molecules of the substances whose reactions are so markedly influenced.

Both vitamins and hormones are products of cell metabolism,* just as are enzymes. There is this difference to be noted: Every cell can apparently synthesize the enzymes it requires for its own metabolism, while many kinds of cells are unable to synthesize the hormones and vitamins they require, and are dependent for their supplies on other cells which can synthesize these compounds. There is a good deal of evidence to indicate that the power of synthesizing vitamins resides only in plant protoplasm (for the single known exception to this rule, see page 196). Hormones, on the other hand, can be produced by animal cells. In the higher animals certain groups of cells are specialized for the production of certain definite hormones, which are distributed from their place of origin over the entire body by means of the blood. Some of the hormones influence metabolism moment by moment. That is to say, changes in the concentration of these hormones are reflected immediately in an altered metabolism. Other hormones, and all vitamins, reveal

* Vitamin D is an exception.

their effects only gradually, demonstrable changes in metabolism appearing some time after the concentration of the hormone or vitamin has been altered. It has been suggested for these latter that they may serve as raw materials for enzymes. Assuming that enzymes waste away very slowly, minute quantities of replacement material might suffice to maintain them. One should not lose sight of the fact that different kinds of cells differ markedly in details of metabolism, and, in agreement with this, differ also in their demand for particular hormones and vitamins. Some hormones seem to serve only the peculiar needs of highly specialized cells, while others appear to be essential to a great variety.

Metabolism Summarized.—Viewing protoplasm as a system we see it to contain a series of substances capable of the reactions of hydrolysis and synthesis; also the specific enzymes by which these reactions are catalyzed. It should be noted that the same enzyme which catalyzes any hydrolysis also catalyzes the accompanying synthesis. Oxidizable substances (and in animal tissues oxygen) are present likewise, together with the hydrogen transporters on which physiological oxidations depend. Some of the substances produced through hydrolysis or synthesis enter at once into other, endothermal, reactions, utilizing energy made available through the physiological oxidations going on in the protoplasm, and giving rise to compounds of high energy value. Some of these compounds, in turn, decompose under suitable conditions, restoring to the system for use the energy locked up in them. In these complex series of reactions hormones and vitamins are involved, either directly or indirectly. In animal protoplasm the general energy balance is negative; in other words, exothermal reactions predominate. A necessary consequence of this is a constant using up of materials of high energy value, with a corresponding production of compounds of lower energy value. Metabolism cannot continue unless the materials consumed are replaced from the outside, and those produced are got rid of, either by being passed to the outside or occasionally by being precipitated within the cells.

It is of utmost importance in picturing metabolism to keep in mind that the reactions and interactions of which it consists are wholly orderly. The organization of protoplasm is such that under normal conditions every reaction is adjusted to all the others, each playing its definite part in a continuously maintained dynamic equilibrium. The sum total of the chemical activity not only keeps the protoplasm in the living state, but achieves the formation of additional protoplasm, which is growth, and provides for all the special functions of which protoplasm is capable. It is in a chemical and physico-chemical organization which automatically guarantees these adjustments that the secret of life resides.

Summary.

The sum total of the chemical activities occurring in living protoplasm are covered by the term *metabolism*.

Chemical reactions included in metabolism are classified as: (*a*) Simple adjustments for the restoration of equilibrium; (*b*) reversible decompositions and syntheses, without much energy involvement; (*c*) exothermal decompositions of substances of high energy value; (*d*) endothermal syntheses of substances of high energy value from components of low energy value; (*e*) exothermal combinations of the sort typified by oxidation.

Both exothermal and endothermal reactions occur in animals, the general balance being in favor of exothermal.

The ultimate source of the energy exhibited by nearly all living things is the sunlight. This is made available through the formation of hexose sugar in the reaction of photosynthesis, a reaction that goes on only in green plants.

The potential energy of hexose sugar and its derivatives is made available chiefly through biological oxidation. In its end stage this is a reaction in which molecular oxygen enters into combination with carbon or hydrogen. The reduction potentials of systems composed of tissue fuel and molecular oxygen under the conditions prevailing in protoplasm are not high enough for combination to occur directly. An intermediary agency of some kind is necessary.

According to the Wieland theory, the carbon atoms present in the fuel substance combine with oxygen atoms derived from the surrounding water, thus leaving hydrogen in surplus; the hydrogen is then removed by union with a "hydrogen acceptor." Subsequently the hydrogen acceptor transfers its acquired hydrogen to molecular oxygen, acting thus as a *hydrogen transporter*.

Two substances, *glutathione* and *thyroxin*, have been identified as probable hydrogen transporters in animal tissues. Others probably occur as well.

Hydrolysis, and its converse reaction, dehydration synthesis, go on simultaneously in any system in which all the substances involved are soluble. The equilibrium reached is a dynamic equilibrium, in which the opposing reactions balance one another. In such a system as protoplasm, with a high water content, the equilibrium point is near complete hydrolysis. To obtain absolutely complete hydrolysis or extensive synthesis one or more products of the reactions must be removed by some means.

Hydrolysis and the opposing dehydration synthesis are catalyzed by enzymes. One enzyme catalyzes both reactions, although any given enzyme is specific with respect to the kind of substance on which it will act. The equilibrium attained under the action of an

enzyme is in general the same as would have been reached if no enzyme had been present.

Enzymes behave like monovalent ions; since they are almost certainly protein or nearly allied substances this implies the establishment of the Donnan equilibrium, and leads to the conclusion that enzyme action may depend, in part at least, on the physico-chemical (micellar) organization of the enzymes.

Enzymes do not enter chemically into the reactions they catalyze. Slight changes in hydrogen-ion concentration affect them materially. They are unstable, losing their catalyzing power more and more as the temperature is raised above room-temperature levels, and being completely destroyed if kept at 60° to 80° C. for one-half hour.

Additional substances known to influence metabolism are vitamins and hormones. The mode of action of these is obscure. Vitamins are produced only by plants and must be obtained by animals in their food (a single exception to this rule is known). Hormones are produced by specialized cells and distributed from their places of origin to all parts of the body by the blood. Normal metabolism cannot proceed unless the vitamins and hormones essential to the particular tissue are present in correct, although minute amounts.

Any given specimen of protoplasm must be pictured as the seat of all the types of reactions listed in this chapter. In animal protoplasm the general energy balance is negative; that is to say, the metabolism is predominantly exothermal. This implies continuous using up of substances of high energy value, and continuous production of other substances of lower energy value. For metabolism to continue the materials consumed must be replaced from the outside, and those produced must be got rid of; also for the most part to the outside.

The organization of protoplasm is such that each reaction proceeds in relation to all the others, maintaining a dynamic equilibrium. Protoplasm is a physico-chemical system which automatically guarantees this adjustment of the reactions to one other.

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CHAPTER IV.

METABOLISM: THE CAPACITIES OF PROTOPLASM.

In describing the organization of protoplasm in Chapter I, stress was laid on the view that the physico-chemical system which is protoplasm would necessarily settle into a state of static equilibrium if the only forces acting were physical. Since the essence of life is the continuous maintenance of a dynamic state, there must be other than purely physical forces concerned in the life processes. These forces are chemical; they constitute part of the entire series of chemical processes which make up metabolism. Other parts of the series may be processes concerned with growth or with the performance of the various functions of which protoplasm is capable.

BASIC METABOLISM.

For convenience of description the expression *basic metabolism* is used to cover the chemical reactions that occur in living cells in connection with the immediate maintenance of the living state, as distinguished from reactions associated with growth or functioning. For illustration, consider adult skeletal muscle: this tissue may be wholly at rest and not be growing; it is the seat, nevertheless, of continuous chemical processes. The presence of these can be readily demonstrated. They are interpreted (Warburg) as the means by which, in the protoplasm, a condition of dynamic equilibrium is kept up. The suggestion is that the free surface energy, whose presence within the protoplasm is the essence of the living state, is thus maintained.

The reactions are predominantly exothermal, as is proved by the fact that there is continuous evolution of heat within skeletal muscle, even though it is wholly at rest. There is also continuous production of carbon dioxide, provided oxygen is available. Muscle is used to illustrate basic metabolism because we have in it a clear example of a structure capable at any moment of doing active work, and kept in readiness for so doing by a continuous expenditure of chemical energy within itself.

Resting Metabolism.—All kinds of tissues display basic metabolism, and in all the significance is the same, so far as we know, as in muscle, namely, keeping the tissue in a state of readiness to function. The distinction between basic metabolism and the metabolism of function is not always so sharp as in muscle, but it

exists nevertheless. Heat production and evolution of carbon dioxide go on in all tissues in rest as well as in activity, although the amount in rest is smaller, as is to be expected. Studies of absolute basic metabolism can be made only in isolated resting tissues. Whole animals, even the very lowest, are seldom completely at rest. Mammals are never so; the heart continues to beat; movements of muscles in the respiratory and digestive tracts are more or less continuous; glandular and nervous activities go on constantly. The closest approach to a determination of basic metabolism that can be had in a mammal requires a state of complete quiet of the skeletal musculature, and a long enough interval since feeding so that the digestive tract shall be relatively inactive. The total metabolism under these conditions, in an adult, represents the basic metabolism plus an inescapable minimum of metabolism of function. It is a very useful quantity to know, and is frequently determined in man, as well as in other mammals. It is designated as *basal*, or *standard*, or simply as *resting* metabolism. (See Chapter XXIX.)

Energy Liberation and Protein Wastage.—Some facts as to the quantities of material and energy concerned in basic metabolism will be given in Chapter XXIX. At present our interest is in the character of the reactions, rather than their magnitude. We have already seen that basic metabolism involves the exothermal reactions of oxidation, as proved by the production of heat and of carbon dioxide. In animals hexose sugar is known to be the chief substance oxidized, although sugar derivatives (lactic acid) and non-nitrogenous protein residues may serve also. In addition to these energy-yielding reactions, basic metabolism includes, in all living tissues, so far as can be judged, another series of reactions in which proteins are involved, and whose effect is a *continuous wastage of protein from every cell*. The basis for the above statement is the fact, to which there is no known exception, that if supplies, either of suitable protein or of utilizable raw materials from which protein can be constructed, are denied to any living cell whatsoever, that cell will go into a decline and finally starve to death, no matter how abundantly it may be supplied with all the other materials required for its metabolism. (It should be borne in mind, of course, that cells in the condition of "suspended animation," as seen in dry seeds and in spores, may endure deprivation of proteins as well as of all other food materials for a very long period). The only conclusion to suggest itself is that protein is continuously lost from all actively living cells, and must therefore be continuously supplied.

In the case of all higher animals direct proof can easily be obtained of a continuous loss of protein from the body; nitrogenous waste-products are important constituents of animal excreta, in starvation as well as in abundant feeding and in rest as well as in activity. Furthermore, animals deprived of protein foods show conspicuous

wasting away of their bulkiest protoplasmic tissues, the muscular tissues (page 184). Hand in hand with the reactions leading to protein wastage go other reactions of protein repair. If the food fails to furnish the necessary constituents for this repair the less immediately essential tissues, particularly the skeletal muscles and the liver, are drawn upon to support those that are more immediately concerned with the preservation of life, such as the heart and brain.

Taken as a whole, the evidence that protoplasmic wastage and repair is an essential part of basic metabolism is impressive and is generally accepted. As to its meaning in the life processes we have no information. Apparently in the stress and strain of keeping free surface energy always in readiness some protein molecules are constantly being disrupted. The number suffering this disruption is proportionately very small. It has been estimated that in man about $\frac{1}{1000}$ of the total amount of protein in the body is disintegrated every twenty-four hours. There is a good deal of protein dissolved in the body fluids, and not built into living protoplasm. This dissolved protein does not appear to share in the disintegration, and so the loss from living protoplasm is relatively greater than from the body as a whole. When we recall, however, that the metabolic processes go on continuously, it is clear that only a small fraction of the protein molecules can be involved at any one time. There is interesting evidence, moreover, that the protein molecules are not completely disintegrated, but merely lose some of their amino-acids. In a series of feeding experiments on young white rats Mendel and Osborne showed that health could be maintained for months on a diet containing none of the amino-acid lysine, although this acid is present in animal protein in proportion of 5 per cent or more, and the body is not capable of synthesizing it out of other nitrogenous foodstuffs. No growth could be had on this diet; that is to say, no new protoplasm could be constructed. There seems to be no escape from the conclusion that lysine is exempted from the wastage that goes on in basic metabolism, although an important constituent of the proteins in which the wastage occurs.

GROWTH METABOLISM.

Growth metabolism includes the whole group of reactions by which new protoplasm is brought into being. In nearly all kinds of animals the growth process as a whole includes also the manufacture and laying down of various non-protoplasmic supporting structures. The production of these may conveniently be included within the scope of growth metabolism.

The main constituents of protoplasm, proteins and phosphatides, are compounds of high energy value. Their primary synthesis is necessarily endothermal. In the case of proteins this primary

synthesis is carried on by plants, which alone in Nature have the power to construct amino-acids out of sugar and inorganic nitrogen compounds. The energy for this synthesis is apparently derived from an accompanying oxidation of sugar, since it is known that the energy of sunlight is not drawn upon directly. In other words, amino-acid synthesis is not a photosynthesis. The formation of proteins from their constituent amino-acids is, as has already been pointed out (page 47), a reversible reaction in which not much energy is involved. Animal proteins are constructed always out of amino-acids of ultimate plant origin. Animal protoplasm has a very limited power of converting one amino-acid into another; glycine, the simplest amino-acid, can thus be produced; but this is not an amino-acid synthesis in the proper sense.

Phosphatides, with their large fat moiety, have an even higher energy value than proteins. Plant protoplasm and animal protoplasm as well can synthesize fat out of carbohydrates; the latter synthesis is exemplified in the ability of milch cattle to produce cream on a diet containing no fat (page 188). Gram for gram fat has more than double the energy value of carbohydrate (9.3 Calories as against 4.1). The synthesis of fat is therefore strongly endothermal and must be accompanied by an energy-supplying exothermal reaction. There is evidence that oxidation of sugar is this reaction.

While much of the energy value represented in animal protoplasm is thus seen to be in products obtained in the food, some of it may be the result of endothermal syntheses performed by the growing protoplasm itself. To support these endothermal reactions other, exothermal, reactions must also go on. These are chiefly, perhaps solely, oxidations. The proteins and phosphatides, together with the other cell constituents, have to be organized into the particular patterns which make up living protoplasm. The presence of free energy is a characteristic of these patterns, hence their organization requires the expenditure of energy, just as their maintenance does. In other words, protoplasm as an organized system has a higher energy value than its constituents taken separately. Growth metabolism is similar to basic metabolism in including both exothermal and endothermal reactions, as well as reactions in which not much energy is involved. It differs in being predominantly endothermal. That is, instead of all the energy appearing as heat, as in basic metabolism, some of it is stored as potential energy in the new protoplasm that has been constructed. On page 43 the fact is pointed out that in some way, distinct from its relation to heredity, the nucleus is essential to growth. Presumably its function has to do with the endothermal stages in the process.

Periods of Growth.—All higher animals pass through a definite growth history which begins with the fertilized ovum, passes through

an embryonic period, then a juvenile period, and enters finally an adult stage. During the embryonic period the various specialized tissues are being differentiated, and in all of them active cell multiplication is going on. In man, at or near birth, and the consequent beginning of the juvenile period, cell multiplication is discontinued in some of the most important tissues, notably the muscular and nervous, growth in them continuing as enlargement in size of the individual cells. After the adult stage is reached there is, under normal conditions, neither growth nor cell multiplication except in certain tissues, *i. e.*, the epidermis, the blood-forming tissues and the germinal tissues.

Growth cannot occur unless all the necessary constituents are provided. These include, beside the well-known components of protoplasm, certain vitamins and hormones. So-called vitamin A, the fat-soluble vitamin (page 194), may possibly be definitely related to the growth process, although whether it is so related is not yet certain. The vitamins that primarily influence basic metabolism also affect growth, since failure of protoplasm to carry on its own life normally is bound to disturb its power to grow. There is at least one *hormone* which is definitely related to growth in vertebrates. This is a product of the anterior lobe of the pituitary body (page 207). It stimulates growth of the skeleton specifically; but since the soft parts adjust themselves to fit the skeleton, determines indirectly the growth of the whole body.

Growth in Vitro.—A problem as yet unsolved is the means by which the various growth stages are brought to an end. The embryonic period, in which active cell multiplication goes on, persists for a time and then is superseded by the juvenile, in which there is less cell multiplication, but active cell growth. This, in turn, gives way to the adult stage, in which only a few tissues show either cell multiplication or cell growth. Some light has been shed on this problem by studies on the cultivation of tissues *in vitro*. Harrison showed, about 1906, that various tissues would live and even grow in suitable culture media in glass vessels. Carrel, in 1924, announced that the ability to grow *in vitro*, and by inference, within the body, depends on the presence of special nutritive material. Juice pressed out from masses of *embryonic tissue* is particularly rich in this material, in fact for a long time was the only known source of it; consequently true growth *in vitro* was seen only in embryonic tissue juice, although tissues might remain alive without growth in various nutritive media, and might even show mitotic division, although the total amount of protoplasm in the tissue mass would remain unchanged, the newly-formed cells being half the size of the parent cells from which derived.

Recently Carrel and Baker have found the essential nutritive material for growth to consist of early cleavage products of com-

mon food proteins. Proteoses (page 398) are particularly favorable substances; *in vitro* cultures provided with abundant proteose growing much faster than in the embryonic tissue juice previously used. Prior to this discovery of the specific nature of the materials utilized in growth Carrel had proposed the generic term *trephones* to apply to them. The evidence indicates that in embryonic cells the enzymes present catalyze the early protein cleavages more rapidly than the later; consequently proteoses tend to accumulate to a greater extent than in older cells, in which cleavage extends actively through the peptone stage to that of simple polypeptids or even amino-acids (page 398).

Two kinds of cells appear to retain in the adult this embryonic property of forming trephones (proteoses) out of the proteins present in the culture medium. These are two types of nucleated blood cells, monocytes and lymphocytes (page 260). These retain the power to form trephones and to pour them out into the surrounding medium as formed. The epithelial cells, which continue to grow and multiply throughout life, appear to be nourished by the blood cells. The trephones are not catalysts nor growth stimulants, but true providers of protoplasmic substance. Their existence strengthens the distinction between basic and growth metabolism, since they constitute, apparently, an indispensable stage in growth metabolism, while not concerned in basic metabolism. Their role in relation to the increase in size of such tissues as muscle and nerve during the juvenile period of growth is as yet unknown. They have been shown to function in a particularly interesting manner in connection with the proliferation of connective-tissue cells (fibroblasts) in the adult. These cells are inactive ordinarily, but in bodily injury, such as leads to the formation scar tissue, become very active, multiplying rapidly. It has been shown that this increase in activity is due to the accumulation of nucleated blood cells in the region of injury, as the result of irritation, and will not occur if their accumulation is prevented. The fibroblasts are cells that retain the power of growth, as do the epithelial cells, but cannot ordinarily display it, because not in sufficient touch with the blood cells on which the trephone supply depends.

One further suggestive bit of information has been derived from the culture of tissues *in vitro*. It has been shown that surrounding such tissues with body fluids from adult animals actually hampers growth, even though other conditions are favorable to it. This is interpreted as meaning that *growth inhibitors* are produced by some or all of the cells and poured out into the body, the production of these being progressively greater as the tissues advance in age; when present in sufficient amount actually preventing growth metabolism from proceeding.

It was pointed out by Minot some years ago that the *rate of*

growth falls off progressively from the very beginning of the life of any individual to its end. Child has related this to a progressive falling off in the vigor of metabolism. It is conceivable that the growth inhibitors revealed by the studies of tissue growth *in vitro* are nothing more than inevitable by-products of metabolism which are of such a sort as not to be eliminated completely, and hence gradually accumulate, and by their mere presence, in accordance with the laws of chemical equilibrium, slow the whole metabolic process. According to this idea the cessation of growth would be merely the effect of these by-products on the special metabolism of growth. Senility would be due to their influence on basic metabolism, and probably on the metabolism of function as well.

FUNCTIONAL METABOLISM.

The point has been stressed repeatedly that the chemical processes by which protoplasm performs the various activities of which it is capable are not identical with those of the fundamental life process or of growth. They are superimposed upon these, and while in many animal forms it is impossible to tell where one set of reactions leaves off and the other begins, the drawing of a distinction seems valid, not only for convenience, but from the standpoint of physiological theory. The designation *functional metabolism* is used to cover the reactions here under consideration.

Three Types of Activity.—When we analyze the complex activities of which animals are capable we find that from the standpoint of protoplasmic function they are reducible to three types, namely, the making of movements, the reception and transmission of disturbances of equilibrium and the manufacture and outpouring of materials. In the higher animals these are exemplified by muscular contraction, by the functioning of sense organs and the nervous system and by glandular activity. Every activity displayed by the body as a whole or by any of its parts can be assigned to one or the other of the above types, singly or in combination.

General Features of Functional Metabolism.—In following chapters each of these types of functional metabolism is discussed in detail. Certain features characteristic of functional metabolism in general will be mentioned here. We have aready seen that through the operation of basic metabolism the protoplasm is kept in a state of readiness to function. In other words, free surface energy is available. Function consists in the utilization of this energy for doing the things that the protoplasm does. The free energy resides in a physico-chemical system in a certain state, and its utilization, in other words, protoplasmic function, is primarily a physico-chemical rather than a chemical process, although chemical reactions may enter to some extent. There is a disturbance of dynamic equilib-

rium, and under the laws of dynamics the system must necessarily proceed to a new equilibrium. This change from an existing to a new equilibrium makes energy available and so establishes function. A characteristic of protoplasm is its ability to function more or less continuously. This implies that after functioning once there is a restoration of the former state of readiness, to enable the protoplasm to function again. *Functional metabolism*, which is chemical activity primarily, constitutes the means by which the system is restored. The reactions are necessarily predominantly exothermal, since they must provide for the restoration of the potential energy released in the functioning. The oxidation of hexose sugar is the chief energy-providing reaction concerned. It should be noted that while restoration of a disturbed system is the essence of all functional metabolism, the actual energy involvement differs greatly in the different types. In muscular contraction energy release is the most significant feature, since the doing of mechanical work is the purpose of muscular action; in sense-organ and nervous functioning the actual amounts of energy displayed are minute, although significent; in glandular activity material rather than energy is in question, and the energy involvement is incidental rather than fundamental.

Summary.

Basic metabolism includes all reactions associated with the immediate maintenance of the living state. These reactions are looked upon as keeping the protoplasm in a condition of continuous dynamic equilibrium in which free surface energy is at all times available. The reactions are predominantly exothermal, and include biological oxidations. Determinations of basic metabolism in mammals are only approximate, on account of the impossibility of avoiding a minimum of function. These approximate determinations are designated as *basal*, *standard* or *resting* metabolism.

In all tissues *basic metabolism* appears to involve reactions whose effect is a continuous wastage of protein from every cell, with the consequent necessity of continuous repair processes. In animals the food must contain the necessary constituents for this repair or the less immediately essential tissues will be sacrificed to support those that are more essential. There is evidence that only a small proportion of the protein molecules in any sample of protoplasm are involved in this wastage at any one time; further evidence that in the wastage the protein molecules are only partially disintegrated.

Growth metabolism includes all reactions by which new protoplasm is brought into being; it may also cover the manufacture and laying down of non-protoplasmic supporting structures. The main con-

stituents of protoplasm, proteins and phosphatides, have high energy value. They are synthesized primarily by plants. Animals have no power to construct amino-acids from sugar and inorganic nitrogen compounds, and only a limited ability to construct the constituents of phosphatides. Protoplasm as an organized system has a higher energy value than its constituents, taken separately. Growth metabolism includes both endothermal and exothermal reactions. The former predominate. The relation of the nucleus to growth is probably in connection with the endothermal stages of the process.

Certain vitamins and hormones appear to be concerned in growth metabolism; the mode of their action is obscure. Fat-soluble vitamin A and a hormone produced by the anterior lobe of the pituitary body are examples of substances having this relationship.

Studies of tissue growth *in vitro* have demonstrated the existence of essential intermediary substances in growth metabolism to which the name *trephones* has been assigned. Trephones are proteoses; they supply actual nutrition; they are not hormones nor catalysts. They are produced by embryonic tissues in connection with their metabolism. No adult tissues are known to produce them except certain nucleated blood cells, monocytes and lymphocytes, which remain embryonic in respect to this property. Adult tissues, like fibroblasts and epithelial tissues, which retain the power of proliferation, are nourished by blood cells; unless so nourished they will not grow.

In vitro studies have demonstrated also that adult body fluids contain substances inhibitory to growth. These may conceivably be merely by-products of metabolism which are not completely eliminated and whose accumulation slows the metabolic processes in accordance with the ordinary laws of chemical equilibrium.

Functional metabolism includes the reactions associated with the performance of the activities of which protoplasm is capable. In animals these activities reduce to three types, namely, the making of movements (muscular contraction), the reception and transmission of disturbances of equilibrium (sense-organ and nervous functioning) and the manufacture and outpouring of materials (glandular activity).

Function consists in utilization of the free energy resident in the protoplasm. This is primarily a physico-chemical, and only secondarily a chemical, process. The equilibrium is disturbed and the system proceeds to a new equilibrium. Functional metabolism, which is primarily chemical activity, is the means by which the system is restored to its former state, and so is ready to function again. The reactions are predominantly exothermal, oxidation of hexose sugar being prominent. In muscular contraction energy

release is the significant feature; in sense-organ and nervous functioning the energy display is minute, but undoubtedly significant; in glandular activity material rather than energy is in question; the energy involvement is incidental.

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CHAPTER V.

STIMULATION: THE CONTROL OF FUNCTION.

Importance of Control of Function.—In Chapter IV it was seen that functioning in living cells involves a disturbance in the dynamic equilibrium which basic metabolism tends to maintain. In some forms, particularly those low in the scale, and in some tissues, even in the highest forms, the disturbance appears to be spontaneous; as the processes of functional metabolism operate to restore these tissues following activity on their part, the equilibrium becomes increasingly unstable, and presently, without any influence from without, function recurs. It is generally true that with increasing specialization of particular tissues automaticity disappears. Hand in hand with this, however, goes increasing development of mechanisms for the control of function. Thus in the higher animals successful operation of the body as a whole requires that most of the specialized tissues be under definite control in respect to function. In order for this control to be possible function cannot be spontaneous, but must depend on some definite inciting agency. Furthermore, the control of function involves the possibility of bringing to a stop activities that are in progress, as well as starting them in quiescent tissues.

IRRITABILITY AND STIMULATION.

The property of tissues by virtue of which they respond to outside influences, either by beginning to function or by ceasing to do so, is called *irritability*. Any agency that serves to evoke irritability is known as a *stimulus;* the action of the stimulus is *stimulation*. It may take the form of *excitation*, when function is initiated, or of *inhibition*, when function is suppressed.

Excitation Results from Change in Cell Membrane.—To form a picture of how excitation is produced it is necessary to recall the account of the cell membrane and its properties as given in Chapter II. The cell membrane was there described as an equilibrium membrane, determined in character by the kinds and proportions of materials present within and without the cell; displaying the Donnan equilibrium, because including both non-diffusible and diffusible ions; and subject to alteration in permeability as different influences are brought to bear upon it. An important part of the conception is that the general equilibrium of the system involves the cell protoplasm reciprocally with the membrane. That is, just

as changes in the protoplasm are reflected in the membrane, so changes in the membrane bring about alterations in the protoplasm. We can state this same idea in other words by saying that the dynamic equilibrium within the cell is dependent on the integrity of the cell membrane, and is likely to be upset by changes in the latter.

In Chapter IV we saw that function is the consequence of a disturbance of the existing dynamic equilibrium. This, taken together with the last paragraph, connects excitation, which is the initiation of function, directly with changes in the cell membrane. According to this view, any agency which will so affect the cell membrane as to induce an upset in the dynamic equilibrium within the cell protoplasm is an exciting stimulus. When the agencies that are known to act as excitants are examined they are found, without exception, to be capable of bringing about changes in cell membranes. Many of them have been shown experimentally to have this effect. It should be noted that in excitation the change is always in the direction of *increased* permeability. The conclusion drawn is that the increased permeability permits an escape of ions previously held, and that the equilibrium is upset as the result of this escape.

CLASSES OF STIMULI.

Not all the energy manifestations surrounding an organism are capable of acting as stimuli. Those that are effective are classified as follows: (*a*) Mechanical (including actual contact and sound waves); (*b*) thermal; (*c*) photic (including all stimulating effects due to radiant energy); (*d*) electrical; (*e*) physico-chemical (perhaps identical with *d*); (*f*) nervous. Class *d*, electrical stimuli, are very effective excitants, but occur rarely in the normal environment (lightning is too destructive to rank as a stimulus), and correspond to no specially adapted receptive structures, as do the other types of stimuli. Nervous stimuli (class *f*) are probably physico-chemical or electrical in reality, but in the absence of definite knowledge are classified separately for the time being.

Stimulation Implies Energy Change.—A fact of fundamental importance in connection with stimulation is that the steady impact of energy is less likely to be effective than a *change of energy*. One result of this is that protoplasm commonly responds well to the *onset* of any new energy relationship, but if the relationship continues, even though it involves a continuous flow of energy into the organism, the stimulating effectiveness quickly declines (page 488). It is not difficult to see why this is so; suppose, for instance, a cell to be under a particular mechanical pressure; the cell boundary takes on an equilibrium which is an equilibrium only for this particular pressure; any change in pressure, whether an increase or a

decrease, disturbs the equilibrium, brings about a change in membrane permeability and if pronounced enough constitutes excitation. Thermal stimuli, which are sharp changes of temperature, presumably bring about sudden changes in the rate of movement of some or all of the surface molecules, increasing the size of some or all of the interstices in the membrane, with the effect of increasing its permeability.

Photic stimuli, sudden increases or decreases in the intensity of light, are known to act in the eye through the intervention of substances decomposed by light (photolabile substances), of which many are known in chemistry. The action on the protoplasm is thus physico-chemical (or electrical) and only indirectly photic. Many animals in which neither photolabile compounds nor specialized eyes can be demonstrated nevertheless take definite positions in relation to sources of light (so-called phototaxis), and in such we assume a direct excitation of the protoplasm by light. Radiant energy of markedly shorter wave length than light is very generally destructive to protoplasm, a fact that is taken advantage of in the treatment of malignant growths by roentgen-rays and radium. Ultra-violet radiation (with wave lengths just too short to excite the human eye) has definite effects on protoplasm, seen in the skin changes of sunburn and of becoming "tanned;" also in connection with the synthesis of vitamin D (page 196). Neither of these actions can be considered excitation, in the sense in which the word is used here.

Physico-chemical and *electrical* stimuli, exemplified in the one case by strong solutions of electrolytes, and in the other by ordinary electric shocks, are believed to act through effects on the Donnan equilibrium. We have noted that this equilibrium establishes definite electric stresses between the cell surface and the surrounding medium. The passage of an electric current through and among cells is necessarily accomplished by movements of ions. These ionic movements are bound to involve upsets in the prevailing ionic equilibrium, which is in large part the Donnan equilibrium. Thus the surface membrane is affected and, as experiment shows, in the direction of increased permeability. Solutions of electrolytes may have similar effects in disturbing ionic equilibrium. If the disturbance is such as to increase permeability the solution may act as an excitant.

The Action Current.—Excitation is always accompanied by an electrical change at the excited point by which that point becomes of lower potential than adjoining unexcited parts of the tissue. If an electrical conductor with a sensitive galvanometer in circuit is placed so as to connect an excited with an unexcited point, a current will flow from the unexcited to the excited region. This current was discovered long before its source and nature were understood,

and was named the "action current," being associated at first with the functioning which results from excitation, rather than with the excitation proper. To explain the lowering of potential at an excited point we have to recall that the surface membrane displays the Donnan equilibrium, and since the non-diffusible ions present are anions is charged negatively with respect to the surrounding medium (page 23). The various parts of the membrane are, however, equal to one another in potential, all being negatively charged to the same degree. Diffusible cations, bearing positive charges, are more concentrated within the membrane than without it, and when the permeability of the membrane is increased there is an escape of positive ions to the outside, lowering the potential of the membrane in this region below the former level, and so below that of unexcited regions. This potential lowering, which can be detected in the form of the action current, is believed to be an invariable accompaniment of excitation under normal conditions, and is much used as a test of the presence of excitation, particularly in tissues such as nerve, which show no visible change when functioning. When a tissue is injured there is a similar escape of positive ions at the region of injury, leading to a local lowering of potential which can be detected in the form of a "current of injury."

Methods of Excitation.—For the artificial excitation of tissues in experimental physiology, electric shocks are more used than any other type of stimulant. It is necessary, therefore, to describe briefly the various methods of stimulating tissues by electricity. A method that is almost ideal in theory is by means of condenser discharges. These have high potential and correspondingly high stimulating effectiveness. They do not injure tissues if the potentials are kept within reasonable bounds. The energy contained in the shocks can be accurately known. In practice condenser discharges are troublesome to handle, and require much equipment if stimuli over a wide range of effectiveness are to be used.

Ordinary direct currents will stimulate tissues if of high enough potential to overcome the high electrical resistance of tissues. They are not injurious if the *quantity* of current is kept small. The conduction of electricity through tissues is by movement of ions, as already pointed out, and stimulation occurs only at the beginning or cessation of such movement. The passage of a steady current through a tissue involves the movement of steady streams of ions; cations toward the cathode and anions toward the anode. The surge of cations toward a membrane in the region of the "physiological cathode," *i. e.*, the point where the current leaves the tissue, causes the excitation when the current starts; the backward surge of the same ions toward some membrane in the region of what was the "physiological anode" (the point where the current enters the tissue) during the period of current flow explains the excitation that

occurs when the current is broken. This latter excitation is necessarily much less intense than the former.

If the stimulating current is applied to the tissue directly by means of metallic electrodes, the movement of ions is very soon blocked by their piling up at the electrodes, and so the current can no longer pass. This effect is known as polarization. It can be prevented by the use of electrodes which do not interfere with the free movement of the ions by which the current is carried. Such electrodes can be constructed by the use of a metal dipping into a solution of its own salt. Zinc dipping into a saturated solution of zinc sulphate is ordinarily used. The zinc sulphate cannot be allowed to come into contact with the tissue, so a thread soaked in sodium chloride solution is passed from the vessel of zinc sulphate to the tissue, or in some forms the electrode vessel is composed of porous clay which is soaked in sodium chloride before use, and then applied directly to the tissue, the sodium chloride acting as a shield to prevent the zinc sulphate within the electrode from coming into contact with the tissue.

Chronaxie.—In excitation with direct current two factors enter, current strength and time. A strong current may excite if allowed to flow only for an instant, while a weak current must flow for a longer time. The least current that will excite if left on indefinitely is designated the *rheobase*. The minimum time at which a current just double the rheobase will excite is known as the *chronaxie*. This is shorter the more sensitive the tissue; hence is a valuable index of relative sensitivity. The chronaxie of most nerve fibers is of the order of one thousandth second; while the chronaxie of smooth muscle is around one-tenth second.

Induction Shocks.—The most convenient and most used means of exciting tissues electrically is by means of induction shocks. In the apparatus for generating induced currents for use in the physiological laboratory (Fig. 4) the primary coil is an electro-magnet of low resistance, with few windings; the secondary coil has many windings of fine wire and high resistance (10,000 turns, and 1000 to 1500 ohms resistance are frequent standards). Shocks are generated by making and breaking a constant current through the primary coil. At each such make or break there is induced in the secondary coil a current which rises sharply from zero to a maximum and immediately decays, but much less sharply. The stimulating effectiveness depends on the height of the maximum and the quickness with which it is reached. When a primary current of low voltage, as from a battery, is used, the shocks produced at the break of the primary current rise much more steeply and to a higher point than those at the make. This is because self induction in the secondary coil can exert its full opposing influence at the make, but only that part of it represented by the sparking at the key at the break.

The result of this is that "break" shocks are usually several times more effective than "make" shocks. The higher the voltage of the primary current the more nearly will make shocks equal break shocks. The maximum height to which the "induced" current will rise depends, in any given inductorium, partly on the intensity (that is, the ampèrage) of the primary current, increasing in proportion to the intensity, and partly on the position of the secondary coil with reference to the primary. In general, the further away the secondary coil is placed the lower will be the maximum height of the induced current. This fact is taken advantage of as a convenient means of varying the effectiveness of induction shocks.

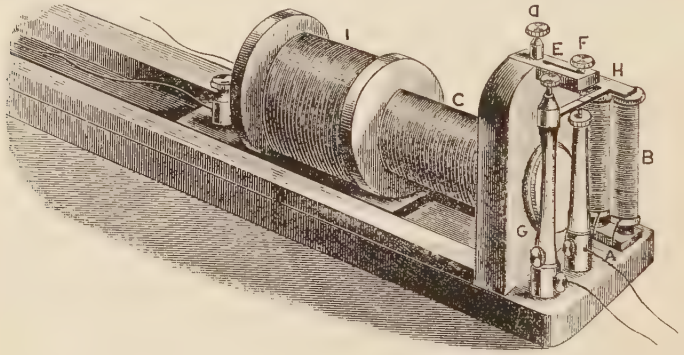

FIG. 4.—Diagram of inductorium. *C*, primary coil; *I*, secondary coil; *EHB*, arrangement for making and breaking the primary circuit automatically sixty to one hundred times a second. (Hall's Experimental Physiology.)

The secondary coil is mounted on a slide, so that it can be placed directly over the primary, or moved any desired distance away. It is possible to prepare a calibration by which the relative strengths of shocks at various positions of the secondary coil can be compared. Induction shocks have very high voltage, but the actual amount of current moving is exceedingly small; the time occupied is also very brief, not exceeding a few thousandths of a second. Make shocks are opposite in direction to break shocks. In consequence of these facts induction shocks are not injurious to tissues, and they will not have any polarizing effect when repeated in rapid succession, provided both make and break shocks are allowed to pass through the tissue. Metallic electrodes (platinum preferred) are satisfactory for use with induction shocks.

NERVOUS STIMULATION.

In all animals except the very simplest the active tissues are controlled chiefly through nerves, which are cells specialized for that purpose. Very little is known about the way in which nervous

stimulation is actually carried out. In harmony with the general view that stimulation is due to alteration in cell-membrane permeability it is assumed that the stimulation effected through nerves operates by bringing about such alteration. With regard to the mechanism we have no information.

INHIBITION.

Inhibition, or the suppression of activity, has already been mentioned as a cardinal feature of the control of function which makes possible the successful operation of the complex bodies of the higher animals.

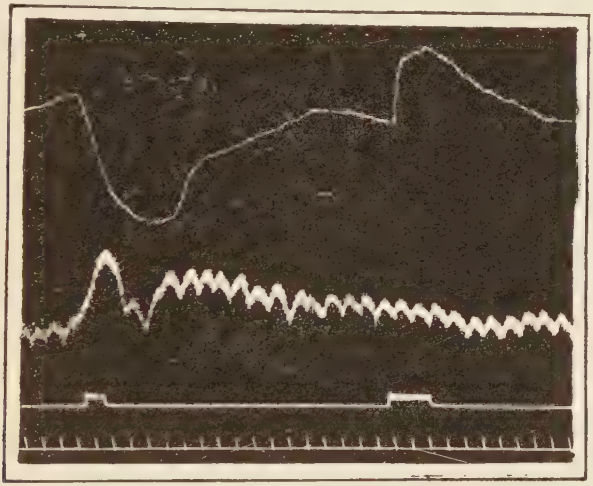

FIG. 5.—Effect on tongue volume of stimulating an excitatory nerve to the musculature of the tongue bloodvessels (vaso-constrictor effect) and of stimulating an inhibitory nerve to the same vessels (vaso-dilator effect). The drop in the upper line marks the decrease in volume due to excitatory stimulation; the rise in the line marks the increase in volume due to inhibitory stimulation. The excitatory stimulation lessens the volume of blood in the organ; the inhibitory stimulation permits more blood to enter. The other tracings in order are: Record of general arterial pressure; signals indicating instant of applying stimuli; time in ten-second intervals. (Bayliss' Physiology, Longmans, Green & Co., Publishers.)

Such evidence as has been obtained supports the view that inhibition is due to alteration of the cell membrane in a direction opposite to that which causes excitation. In other words, the membrane is made less permeable. In the body inhibition is brought about through nervous action. The nerves that cause this effect are usually not the same as those that cause excitation, and there is evidence that the two sets of nerves make contact with the tissue cells at different points.

An example of the opposed action of excitation and inhibition is

shown in Fig. 5, where the stimulation of a nerve which caused *excitation* of the muscles in the walls of the small arteries of the tongue resulted in *decrease* in tongue volume, while stimulation of another nerve which caused *inhibition* of the same muscles resulted in *increase* in tongue volume.

RECEPTORS.

So far as the body as a whole is concerned the control of function must be in relation to the environment at large. The preservation of life on the part of the individual, and of the race on the part of the species, involves a continuous series of adjustments of animals to each other and to organic and inorganic nature as a whole. Food must be obtained; inclemencies of climate withstood; bodily injury avoided; the propagation and care of offspring achieved. All these require the existence of means whereby the individual shall be impressed by the environment, as well as of means for making the necessary responses. In the higher animals the environment impresses itself through specialized structures, known collectively as *receptors,* and more familiarly as sense organs. The peculiar property of these, as a group, is that they are more susceptible to stimuli than undifferentiated protoplasm is. Furthermore, individual sense organs are specialized to respond with especial sensitiveness to particular kinds of stimuli. The eye, for example, responds to light; the ear to sound; certain receptors in the skin to thermal stimuli. The stimuli produce excitation in the cells of the sense organ. This is passed on at once to nerves for transmission to the active tissues by which the adjustments to the environment are to be performed. Since receptors are able to pass stimuli on to tissues less sensitive than themselves building-up processes of some sort seem to be implied; we consequently assume the receptors to carry on their own special types of functional metabolism (page 474).

Summary.

The property of tissues by virtue of which they respond to outside influences is called *irritability.* Any agency that evokes irritability is a *stimulus;* the action of the stimulus is *stimulation.* It may take the form of *excitation,* when function is initiated, or of *inhibition,* when function is suppressed.

Excitation is looked upon as due to an alteration in the cell membrane whereby its permeability is increased. The increase in permeability permits an escape of ions, which in turn upsets the previously existing dynamic equilibrium, and so initiates function.

The classes of exciting stimuli are: (*a*) Mechanical; (*b*) thermal; (*c*) photic; (*d*) electrical; (*e*) physico-chemical; (*f*) nervous.

Since the Donnan equilibrium prevails in the cell membrane, and the non-diffusible ions present are anions, the diffusible ions that are in excess are cations. When the permeability of the membrane is increased in excitation these are the ions that escape. The result is a local lowering of potential which may be detected as the "action current."

Injury to a tissue brings about conditions leading also to an escape of cations, establishing a similar local lowering of potential, which may be detected as the "current of injury."

Tissues are excited experimentally chiefly by means of electric shocks. These may take the form of condenser discharges, or of the making or breaking of a constant direct current, or of induction shocks. Details of each method are given in the text.

Inhibition, or the suppression of function, is supposed to be the result of a change by which the cell membrane becomes less permeable.

In the body as a whole the control of function in relation to the environment is based upon the operation of *receptors*, or, as they are more familiarly known, sense organs. These are specialized tissues which are peculiarly susceptible to particular classes of stimuli. The disturbances of equilibrium which excitation causes in the cells of these receptive tissues are passed on at once to nerves. Since the receptors are more sensitive than the nerves they excite they are considered to display functional metabolism.

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CHAPTER VI.

CONTRACTION.

AMŒBOID MOVEMENT.

An important characteristic of animals is their ability to make active movements. This ability is based on the property of converting potential energy present in protoplasm into energy of tension. The tension or pull may cause movement of the body as a whole or of some part of it, in which case work is done; or it may fail to bring about any movement, in which event the energy is all converted into heat. In amœba and similar protozoa, and in certain cells in higher animals (so-called amœboid cells), the cell surface is the seat of the development of tension; in these cells changes in ordinary surface tension are thought to be responsible for the movements. They consist essentially of protrusions and corresponding withdrawals of parts of the cell, as the result of which its shape changes continually as long as activity persists. Movements of this sort are known as "amœboid movements." If the protrusions are persistently in one direction the cell travels forward. Such migrations are frequently seen in leukocytes (page 258).

CILIARY MOTION.

In ciliated cells the development of tension is in the cilia and occurs alternately first along one face of each cilium and then along the opposite one. The effect is to make the cilia bend forward and back rhythmically. The development of tension is sharper along one face than along the other, making the beat of the cilia more forcible in one direction than in the reverse. The mechanism of tension development in cilia is not understood; nor is much known about the very interesting arrangement which causes all the cilia in any one cell to beat in harmony. Ciliated surfaces occur in the human body, particularly in the lining of the bronchial passages and in the Fallopian tubes.

In all the higher animals active movements are based on the development of tension in muscular tissues. Three classes of muscle tissue are recognized, skeletal, smooth and cardiac. The three types present structural and functional differences so marked as to make it necessary that each be considered by itself.

STRUCTURE OF SKELETAL MUSCLE FIBER.

Skeletal muscle is the most highly specialized of the contractile tissues, and serves best for a first description of muscular action. The unit is the muscle fiber, which is a multinuclear cell, cylindrical in general form (Fig. 6). In man the diameter varies between 10 and 100 μ (microns) and the length from a very few millimeters up to about 35 to 40 mm. The fiber consists of: (*a*) The *sarcolemma*, which is an enclosing membrane of great delicacy, but permanent, and not identical with the protoplasmic cell membrane; (*b*) the *fibrils* or *sarcostyles*, which are longitudinal cylinders apparently of relatively dense protoplasm; (*c*) the *sarcoplasm*, which is the fluid occupying the space among the fibrils. In the muscle as a whole

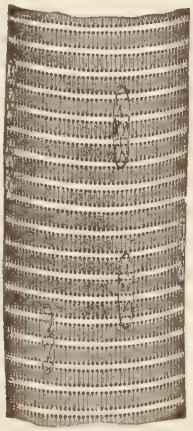

FIG. 6.—Portion of a single skeletal muscle fiber (mammalian) examined fresh in serum, highly magnified. (From Schäfer's Essentials of Histology, by permission of the author.)

the individual fibers are bound together by a connective-tissue framework, which pervades and envelops the whole mass. The sarcolemma of each fiber is the means by which the tension developed within it is transmitted to the outside, and so made effective. The individual sarcolemmas merge into the connective-tissue framework, and thus find attachment. The pervading connective-tissue framework, in turn, merges at the ends of the muscle into the stout and inelastic tendons by which the muscle is attached. In the case of such muscles as are attached directly the merging is with the periosteum.

The *sarcoplasm* has apparently the ordinary features of watery protoplasm. Its chief special characteristic, so far as known, is the presence of glycogen $(C_6H_{10}O_5)_n$ in concentrations as great as

1 per cent of the weight of the muscle (page 84). This represents an available store of carbohydrate fuel.

The *fibrils*, as already stated, appear to be dense cylindrical condensations of protoplasmic substance lying lengthwise within the fibers. All methods of histological examination agree in bringing out strongly marked cross bands on each fibril. These lie at corresponding levels in all the fibrils, imparting to the fiber as a whole a very characteristic cross-striated appearance. As yet the relation of these conspicuous cross-markings to the act of contraction is a matter of theory rather than of ascertained fact.

In Chapter IV (page 65) the fact is stated that protoplasm is thought to function by releasing surface energy. If this conception holds for skeletal muscle the most probable seat of tension development is the interface between fibrils and sarcoplasm. Also most theories of contraction not based on release of surface energy look on the fibrils as the primary mechanisms of contraction. It is accordingly interesting that the proportion of fibrils to sarcoplasm varies in different types of muscle; those with the largest proportion of fibrils are, in general, most powerful.

Stages in Muscle Action.—Applying to muscle the generalized account of functioning already given (page 65), the steps in contraction are as follows: (*a*) Excitation, leading to an upset in the existing dynamic equilibrium; (*b*) chemical and physico-chemical processes tending toward a new equilibrium; (*c*) the development of tension in or at the surfaces of the fibrils as the mechanical result of stage *b;* (*d*) a continuation or modification of stage *b* leading to the release of tension; (*e*) active functional metabolism, bringing about a restoration of the former equilibrium. For convenience of description stages *b* and *c* together will be called the phase of contraction, stage *d* the phase of relaxation and stage *e* the phase of recovery (Fig. 9). It should be noted that contraction is the usual result of the development of tension, but does not necessarily occur; when one tries to lift a weight that is too heavy for him, the contractile processes occur in typical fashion, although no actual shortening of the muscle may take place. In this case, since no external work is done, the energy developed appears in the form of heat.

It is clear that the analysis of muscular functioning consists in determining what are the chemical and physico-chemical processes making up stage *b;* how these bring about the tension which marks stage *c;* what processes are concerned in the relaxation of stage *d;* what are the restorative reactions of stage *e*, and how they act to reinstate the former condition. The analysis is far from complete. Succeeding paragraphs give a summary of present knowledge.

Experimental Data.—First of all some experimental data useful in the study of muscular contraction will be given. The determinations have been made chiefly on the excised gastrocnemius muscles of recently killed frogs, which muscles lend themselves to such studies because they survive for several hours and behave in apparently quite normal fashion during nearly the whole of the survival period, if kept moist with saline solution. The excised muscle is stimulated directly, usually with induction shocks. It is made to write a magnified record of its own contractions by attaching it to a lever which ends in a writing point in delicate contact with smoked paper. This latter is usually mounted on a

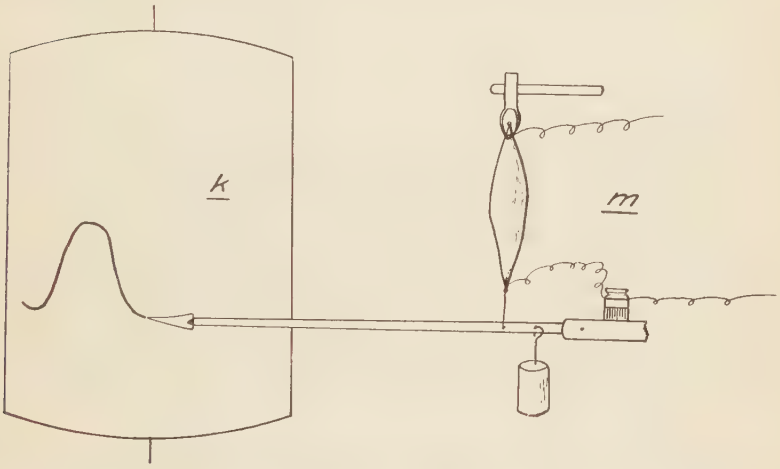

FIG 7.—Diagram of apparatus for obtaining graphic record of muscular contraction. *m*, excised muscle; *k*, drum of kymograph. (Adapted from Stiles.)

drum which may be rotated by hand or driven by a clockwork or other motor. The drum with its driving mechanism is known as a *kymograph*. Other devices for carrying the smoked paper past the writing point are also in common use. The movements of the muscle are so rapid that the eye cannot follow them in detail, and the smoked paper must be in fairly rapid motion. The velocity with which it moves must be accurately known. A tuning fork of known period is usually caused to write its vibrations on the smoked paper simultaneously with the muscle tracing. This gives an accurate time record.

The Simple Twitch.—Under stimulation with a single induction shock a muscle contracts quickly and immediately relaxes; the whole action makes up what is known as a *simple twitch*. Visible shortening does not begin at the very instant of stimulation. There is a delay, called the latent period. In theory this is due partly

to the time required for getting the processes of stage *b* under way. As a matter of fact, however, this part of the latent period is too short to be demonstrated by any ordinary methods, and the latent period seen in the laboratory is due to the fact that the muscle is an elastic structure, which must develop enough tension to overcome the inertia due to its own elasticity before it can begin to move the lever to which it is attached. Under experimental conditions the latent period of frog's muscle is about one-hundredth second. The contraction period, which immediately succeeds, is about four-hundredths second long. The phase of relaxation follows that of contraction without any interval, and may be as brief as five-hundredths second, making the entire twitch take one-tenth second. All these time intervals are subject to change, depending on the temperature, the general condition of the muscle, and whether it has been stimulated much previously.

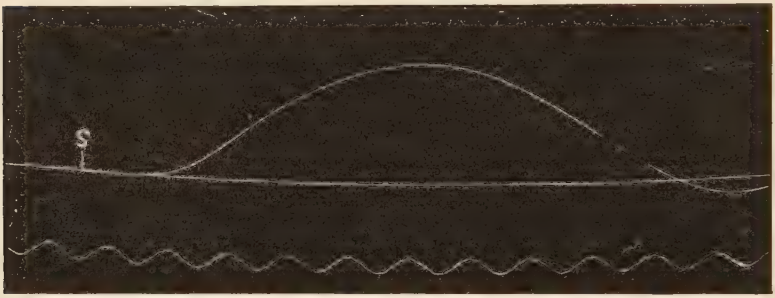

FIG. 8.—Tracing of simple twitch. *s*, instant of applying stimulus. Tuning-fork gives 100 double vibrations a second. (From Howell: A Text-book of Physiology, W. B. Saunders Company, Publishers.)

ISOTONIC AND ISOMETRIC CONTRACTION.

When the muscle lifts a lever, shortening as it develops tension, and pulling against a constant resistance, the contraction is called *isotonic*. The muscle may be caused instead to pull on a strong spring, in which case it shortens very little and the resistance increases as contraction proceeds. This type of contraction is called *isometric*. From the standpoint of the theoretical analysis of the contraction process isometric contractions are more important than isotonic, because the development of tension rather than the actual shortening is the fundamental act in contraction, and this is measured directly in an isometric contraction. In view of the exceeding delicacy of the individual units the force exerted by muscles as a whole is remarkable. The group in the calf of the leg, for example, can pull on the Achilles tendon with a force, in a strong man, of not less than 250 kg.

Muscle Metabolism an Important Fraction of Total Metabolism.—The chemical processes associated with skeletal muscular functioning will be discussed at some length, partly for their intrinsic interest and their importance for any adequate grasp of physiology, and partly because the muscular tissues include by far the major portion of the protoplasm of the body, so that when the muscles function actively the total metabolism is increased to a degree greatly in excess of that to be attained in any other way. When the organization of the body as a whole comes to be studied it will be seen that the provisions for handling this great increase in metabolism are among the most interesting and important bodily features.

MUSCLE, A CHEMICAL ENGINE.

A muscle is a device for transforming energy latent in certain chemical compounds (mainly hexose sugar) into the mechanical energy of muscular work. We have definite proof that active muscles consume more fuel and more oxygen than do resting muscles, and produce more carbon dioxide and water. We know also that there is a chemical process associated with muscular action which results in the production of lactic acid. This substance has long been known to be produced in active muscles. At first thought to be a waste product, it is now looked upon as in all probability of prime importance in contraction.

In accordance with the picture of functional metabolism given previously (page 66) the stage in muscle action in which oxidation occurs is the final one, stage *e*, associated with restoration of the system to its former energy level. The antecedent stages, in which active function is displayed, are anaërobic throughout, depending on chemical and physico-chemical changes in which oxidation processes are not immediately involved.

Lactic Acid Production, the Essence of Stage b.—By several series of brilliant investigations the picture of the contractile process summarized below has been worked out. The reader is referred to the bibliography at the end of the chapter for publications giving details. Stage *b*, given above (page 80) as the stage leading to the development of tension, has as its only known exothermal reaction the production of lactic acid from an antecedent substance of higher energy value. Since the muscle is capable, as the result of the processes of stage *b*, of doing work, it is necessary that the energy liberated during the stage be sufficient to account for the work the muscle can do; otherwise the principle of the conservation of energy is violated. If, as seems to be the case, the process by which lactic acid is formed is the only energy source of stage *b*, it must be exothermal to the extent just indicated.

The most convenient method of determining the energy yield of a contracting muscle is to cause it to perform a pure isometric contraction, *i. e.*, to pull against a resistance too great for it to overcome. When this is done all the energy liberated takes the form of heat, which can be measured by a sufficiently skilful experimenter with great accuracy. It is found that more than one-half the total heat yield occurs during the time tension is being developed, but there continues to be some during and immediately after relaxation (this is independently of the heat of recovery oxidation, which is not here under discussion). The fact that heat production extends over into the period of relaxation is of some theoretical importance, as will appear presently.

Direct experiments, involving determinations of the amounts of lactic acid produced and of the energy liberated in the above type

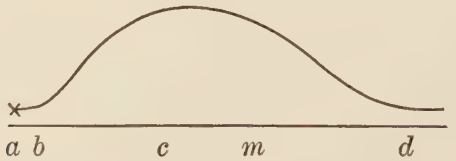

FIG. 9.—Diagram illustrating the sequence of events in a simple muscular contraction. *a*, instant of excitation (Stage *a*); *b-c*, contraction phase (Stages *b* and *c*); *c-d*, relaxation phase (Stage *d*); *m-n*, recovery phase (Stage *e*) (this phase is proportionally much longer than indicated in the diagram. (Martin's Human Body, Henry Holt & Co., Publishers.)

of experiment, have shown that for every gram of lactic acid evolved approximately 370 calories of energy are made available (the unit is the gramcalorie, the energy being stated in heat units, in accordance with prevailing practice, page 454). The chemical relationship of lactic acid to glycogen, of which the muscle has a rich store, is so close that one cannot help but think the former to be derived, directly or indirectly, from the latter. Until very recently there has been a difficulty in the way in that the conversion of glycogen into lactic acid could not be shown to yield the amount of energy (370 calories per gram) necessary to satisfy the requirement. As a matter of fact this reaction by itself, even when brought to its highest energy yield by extreme refinement (Slater) liberates only about two-thirds the above amount; but if to the heat of conversion of glycogen to lactic acid we add the heat of conversion of lactic acid to sodium lactate full agreement is obtained. It is legitimate to include this second reaction, inasmuch as the conditions prevailing in muscle tend to the production of sodium lactate by reaction of lactic acid with basic sodium salts also present (page 87).

There is a good deal of reason to think that the actual immediate precursor of lactic acid is not glycogen, but a compound of it with phosphoric acid, a "hexose phosphate" (Embden). This com-

pound is thought to have energy value virtually equal to that of glycogen itself. There is direct chemical evidence for the existence of hexose phosphate. An argument for its importance is that lactic acid is produced, when the muscle is stimulated, with explosive suddenness, indicating the decomposition of a highly unstable compound. Hexose phosphate might answer this requirement; glycogen seems too stable for the purpose.

Tension Development.—Stage *c*, which is the stage in which the work of the muscle is actually done, is the least understood of any of the stages of which the contractile process is composed. The lactic acid, through its hydrogen ions, is believed to bring about a change, at the interfaces between fibrils and sarcoplasm, or at unidentified interfaces within the fibrils, leading to the development of tension. A. V. Hill has shown mathematically that the change cannot be one of surface tension simply. He suggests rather a change in the electrical stresses prevailing (it is known that mechanical tension can result under suitable conditions from alterations in electrical tension).

A conceivable basis is afforded by a characteristic of protoplasmic micellæ already cited, *i. e.*, the tendency to a decrease in the number of charged ions at the micellar surfaces as the isoelectric point of the constituents of the micellæ is approached. The sudden production of lactic acid shifts the hydrogen-ion concentration in the acid direction, and therefore presumably toward the isoelectric points of the proteins (and phosphatides), of which the micellæ are composed (page 26). The effect is to convert some of the surface proteinate or phosphatide anions into equivalent molecules; the Donnan equilibrium is thus presumably disturbed, and in such a way as to release sodium or other cations, which are then free to react with the lactic acid to form lactates (page 27). There is evidence in support of the idea that some of the cations by which lactic acid is neutralized may be contributed from this source (Meyerhof). Just how the postulated shift in the Donnan equilibrium, with its necessary result of a change in electric stress, acts to causes mechanical tension cannot be stated at present; Hill suggests something in the nature of a sudden "gelation" of some constituents of the protoplasmic colloid.

The "All-or-Nothing" Property.—The *degree* of tension developed in a simple twitch depends presumably on the hydrogen-ion concentration established at the significant interfaces. The hydrogen-ion concentration, in turn, depends on the amount of acid present. The production of lactic acid is necessarily in accordance with the laws of chemical equilibrium. That is, the reaction, once started, proceeds until some sort of equilibrium is reached. It has been suggested (Meyerhof), with evidence in support, that in this case the establishment of equilibrium depends on the attainment of a

certain definite hydrogen-ion concentration. In other words, the reaction is self-limited, hydrogen-ion concentration being the limiting factor. The importance of relating the degree of tension to the attainment of a chemical equilibrium is that it makes the *extent of tension development in individual fibers largely independent of the strength of the stimuli by which they are excited*, provided the stimuli are strong enough to upset the equilibrium prevailing in the resting muscle. This is known as an "all-or-nothing" relationship, there being either a full response to stimulation or none at all. Since wide variations in the extent and force of contraction can easily be induced in whole muscles by varying the strength of stimulation, both in excised muscles in the laboratory and within our own bodies, we are obliged to conclude that different strengths of stimulation may bring different numbers of fibers into play, each fiber responding to its full extent, and the response of the muscle as a whole being determined by the number of fibers involved (see Chapter IX).

Relation of Tension Development to Actual Work Done.—It is important to note that various factors influence the actual work yield of muscles, independently of the number of fibers thrown into play. For one thing, whenever the muscle actually shortens it has to overcome a frictional resistance within its own fibers, due to their viscosity. The energy utilized thus is all converted into heat, and is wasted so far as the doing of external work is concerned. This viscosity factor is more pronounced the more quickly the muscle shortens; it follows that muscles which are free to contract at maximum speed do less useful work in proportion to the energy developed in them than muscles which shorten more slowly. Leaving the nervous system out of account as a factor regulating speed of shortening (page 694), the rate depends on the inertia to be overcome, the greater the inertia the less the speed and hence the greater the efficiency of the muscle. The above statement applies in general to the use of our muscles in doing ordinary mechanical work, but the theory as outlined cannot be applied exactly for the reason that the physiological contractions of muscles in the body are not simple twitches but sustained contractions of shorter or longer duration (page 89). It is true, however, that up to a certain limit our muscles work more efficiently against a load that "feels heavy" than against one that "feels light" (A. V. Hill).

Another important fact is that when a muscle actually shortens as the result of stage *c* the expenditure of energy within it is somewhat greater than when shortening is prevented (Fenn). In other words, for any given strength of stimulus an isotonic contraction is attended by a greater liberation of energy than an isometric, the reason for this is not known.

Relaxation.—Admitting contraction to be due to the production of lactic acid and its presence at certain surfaces on or within the

fibrils, *relaxation*, which constitutes stage *d*, is obviously due to the disappearance of the acid from the same surfaces. The evidence indicates that the acid is got rid of primarily by reacting with basic sodium salts to form sodium lactate (page 91). This compound is known to accumulate in active muscles and to appear in the blood whenever vigorous exertion is performed. The reaction between lactic acid and basic salts is exothermal, and appears to account for part of the energy displayed in an isometric contraction as a whole (page 84). The fact that part of the heat yield of such a contraction occurs after the period of tension development is over accords with this idea.

A feature of relaxation is presumably the recovery from the state of disturbed Donnan equilibrium pictured above as attending contraction (page 85). This implies that as the hydrogen-ion concentration returns to its former value with the neutralization of the lactic acid there is an increase in the proportion of non-diffusible anions (proteinate or phosphatide) in the micellæ and a corresponding fixation of basic cations.

The fact should be stressed that relaxation, as well as contraction, is an anaërobic process. In a fresh muscle it takes place as promptly and efficiently in the complete absence of oxygen as in the presence of a large supply of the same. It is true, however, that if an excised muscle is stimulated repeatedly in the absence of oxygen the relaxation process soon slows down greatly, a phenomenon known as *contracture*. This can be explained without difficulty in terms of the mass law as due to the accumulation of sodium lactate and the resultant hampering of the reactions leading up to its production. Stage *d* is then an important part of muscle function in that it provides for relaxation. Chemically, however, it ranks only as a temporary measure. Unless followed by stage *e*, the stage of recovery, the muscle quickly loses its ability to function normally.

Recovery Oxidation.—Stage *e*, the recovery phase of the contractile act, follows immediately the development of tension. It is apparently set in operation by the same disturbance of equilibrium as initiates stage *b* itself. Stage *e* is the longest drawn out of all the stages; it is barely under way when stage *d* has run its course, ordinarily, and continues for a considerable time thereafter. It can only proceed in the presence of oxygen (or some other hydrogen acceptor), and is, therefore, essentially an oxidation process. The energy furnished by the oxidation serves to restore the high energy values lost from the system in the development of tension. It is always attended by the evolution of relatively considerable heat, showing that the energy set free in the oxidations is only partially used in restoring the system, the remainder necessarily appearing as heat. From the engineering standpoint this means that muscle

is less than 100 per cent efficient. As a matter of fact, the efficiency under most favorable experimental conditions does not much exceed 25 to 30 per cent, and is ordinarily nearer 20 per cent.

The problem of stage *e* is to find out what substance is oxidized and how the oxidation serves to restore the system to its former state. A feature of restoration is getting rid permanently of the lactic acid which is removed from the sphere of action only temporarily by the neutralization taking place in stage *d*. Lactates are themselves oxidizable, and a simple explanation of stage *e* would be to postulate that they are oxidized, thus being removed and providing the needed energy for the restorative process all at one stroke. However, the total energy development of stage *e* can be determined accurately. When this is done, and the amount of energy actually liberated is compared with that which would appear as the result of oxidation of the amount of lactate known to be present, it is found that not more than about one-fifth of the latter can possibly be oxidized. If all of it were burned about five times as much energy would be liberated as actually is. Lactate may be oxidized, it is true, but if so only about one-fifth of the amount produced in stages *b* and *d* is thus taken care of, and the disposition of the remaining four-fifths still remains as much of a problem as ever. The solution came through the discovery that there is a reconversion of lactate into glycogen in stage *e*. This reconversion is an endothermal process; it represents, in fact, the exact converse of the energy-liberating reactions on which tension development is based.

Its accomplishment depends on the supplying of the necessary amount of energy by the accompanying oxidation. The disappearance of all the sodium lactate can be accounted for by the oxidation of some of it and the reconversion of the remainder to glycogen; or it may all be reconverted and the energy furnished by oxidation of some other oxidizable substance or substances, of which the muscle has ample store. Muscles are known to contain or have access to hexose sugar and glycogen and phosphatides, in addition to the lactate present following activity. The simplest view of the choice of fuels is that it is a matter of equilibrium, depending on the relative concentrations of the different fuels in the muscle cells There is, however, some apparently conclusive evidence indicating that the specific reactions of stage *e* depend altogether on the oxidation of carbohydrate material (Furusawa, cited by Hill). Since muscles are known to be able to utilize fatty compounds in their metabolism this evidence implies that fats are converted into carbohydrates before being used in stage *e* (Krogh and Lindhard previously suggested the same idea). In any event fatty substances are utilized in some form or other, in addition to carbohydrates (page 186).

Carbohydrate Equilibria in Muscle.—The carbohydrate materials present in muscle include glycogen in relatively high concentration (about 1 per cent), hexose sugar in substantial equilibrium with the hexose content of the surrounding tissue fluids, *i. e.*, about 0.1 per cent, and hexose phosphate in unknown, but presumably relatively small, concentration. These three substances may be thought of as forming an *equilibrium system*, in which equilibrium prevails when they are present in the relative concentrations indicated. Any disturbance of the equilibrium, as by the sudden decomposition of some of the hexose phosphate, would lead at once to reactions tending to restore the equilibrium. The first step would be reformation of hexose phosphate at the expense of glucose and glycogen. The consequent depletion of these substances would be made good, in part at least, by the resynthesis of glycogen from lactate in the recovery phase of the muscle, stage *e*. The oxidation processes of stage *e* would lead to a further depletion, affecting mainly the glucose. The entire depletion would be made good by entry of additional glucose from the surrounding tissue fluid, with conversion of part of the glucose into glycogen to restore the normal concentration of the latter.

Tetanus.—When muscle is stimulated by a rapid succession of shocks (twenty or more a second in fresh muscle) there occurs, instead of a simple twitch, a sustained contraction known as *physiological tetanus*, or often simply as a *tetanic* contraction. This implies the *maintenance* of a state of tension at the surfaces at which tension is developed, which, in turn, must mean that lactic acid is kept continuously present at the same surfaces. If the view that lactic is produced by explosive decomposition of hexose phosphate is correct, it follows that as the result of each shock part of the hexose phosphate present in the reacting system disappears.

We have to explain the continuous presence of lactic acid in tetanus in the face of the fact that the same stimuli which bring about its production in stage *b* also initiate the processes of stages *d* and *e* which tend to remove it. It is necessary to assume that the synthesis of hexose phosphate from glycogen or glucose, following its decomposition in stage *b*, is so rapid that a second shock, sent in before there has been time for the removal of acid in stage *d* to get under way, finds more hexose phosphate available for decomposition. The lactic acid is supposed to produce its effect by raising the hydrogen-ion concentration at certain definite surfaces. In tetanus we have operating simultaneously stage *b*, which produces acid, and stages *d* and *e*, which get rid of it. The net result is a balance in which, at first, there is enough acid present to maintain a high tension. On account of the relative slowness of stage *e* by which sodium lactate is disposed of, there is bound to be an accumulation of this substance in tetanus, which presently hampers

stage *b* and cuts down the efficiency of the tetanic contraction. Since chemically tetanus is a cycle of acid production and acid elimination it involves a continuous expenditure of energy for its maintenance. The energy-liberating decomposition of hexose phosphate goes on over and over again so long as the tetanus lasts. This type of contraction is important because it is practically the only type seen in muscular activity in the normal human body on account of the way in which the muscles are played upon through the nervous system (page 125).

Fatigue of Muscle.—If an excised muscle is stimulated repeatedly at intervals of about a second for a considerable time (the period required depends on the condition of the muscle), or is given the rapid succession of shocks which causes tetanus for a shorter time, the height of contraction falls off, ultimately to zero, in spite of

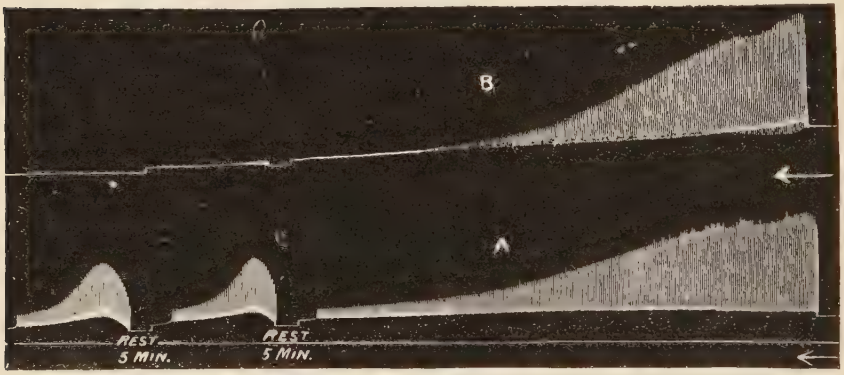

Fig. 10.—Fatigue of excised muscles, stimulated once per second (Fletcher) *A*, in an oxygen atmosphere; *B*, in an atmosphere of nitrogen (oxygen vacuum) (Starling's Physiology.)

continued stimulation (Fig. 10). This loss of contractile power constitutes *muscular fatigue*. It is not identical with general bodily fatigue which will be discussed later (page 736). It is clear that muscular fatigue must be due to failure of the restorative processes which make up stage *e*. If the muscle were completely restored following each stimulation there would be no reason why it should not continue to contract to its full extent until its fuel supplies were exhausted. Stage *e* is primarily based on oxidation. Muscles contain no store of oxygen (page 214); they are dependent from moment to moment on supplies that reach them from their immediate environment. In a complete oxygen vacuum a muscle can contract well for a very short time, but the accumulation of sodium lactate in stage *d* will soon become such that under the mass law relationship the production of acid in stage *b* is no longer possible. This

constitutes complete muscular fatigue. Small amounts of oxygen, insufficient for full restoration, will postpone the onset of complete fatigue. If the muscle fibers are being irrigated by a moving liquid, *i. e.*, the circulating blood, as is the case in the intact body, the products of oxidation will be washed away as fast as formed, and the degree of fatigue that will develop will depend wholly on how nearly the oxygen supply keeps pace with the demand upon it. A so-called *fatigue level* is taken and held for a long time by muscles under this circumstance. If the muscle is excised from the body, so that its individual fibers have no means of getting rid of oxidation products, except by diffusion of carbon dioxide into the air, it will develop complete fatigue, stimulation producing no effect whatever. Such a muscle, if left for a time, recovers to nearly its former power, showing that through the combined inward diffusion of oxygen from the air, and outward diffusion of carbon dioxide from the muscle, stage *e* has been able to proceed to somewhere near its full extent.

Going in Debt for Oxygen.—In very sharp exertion in man the processes of stages *b* and *d* may far outstrip those of stage *e*. A state of marked muscular exhaustion may be thus induced. The muscles and body fluids both become charged with sodium lactate. It has been shown (A. V. Hill) that as much as 4 gm. of lactic acid a second may be produced by a powerful man and as much as 130 gm. may accumulate in the body as a whole before exhaustion brings the exertion to an end.

The lactate circulates everywhere in the blood stream; some of it is eliminated by the kidneys (page 234); the remainder dialyses out from the blood into the various tissues (whether the glandular and nervous tissues take part in this is not known); at first those that had no share in producing lactate are the only ones having a low enough concentration of the substance for diffusion into them to occur, but later the previously active tissues reduce their lactate content to a sufficient extent so that they share in the uptake of circulating lactate. The tissues that take up lactate reconvert it into glycogen by a stage *e* process, as previously described. The important feature of this arrangement is that whenever exertion is so pronounced that a local oxygen deficit occurs in any group of active tissues the body as a whole takes part in the recovery process.

When exertion is as extreme as indicated above the process of recovery is long drawn out, often requiring an hour or more. During all this time extra oxidation is occurring to supply the necessary energy of the restoration process. Since the recovery oxidation can lag so far behind the exertion the body is spoken of as able to "go into debt for oxygen." The amount of this debt may be as much as 18 or 19 liters of oxygen. That is, lactate may accumulate

to such an extent that the above amounts of oxygen are used for getting rid of it, over and above the regular requirements of the body during the recovery period.

Rigor.—Shortly after the death of a muscle it goes into a state of strong and persistent contraction known as *rigor mortis;* the familiar death stiffening is due to this contraction occurring in all the muscles of the body. Muscles killed by heat show the same phenomenon, called in this case *rigor caloris.* Lactic acid is produced in connection with rigor, and the present belief is that the development of tension is due, in rigor as in physiological contraction, to the presence of this acid. Hoet and Marks have recently shown that the disappearance of hexose phosphate is probably also a factor. The state of rigor passes off after some hours, and it can be shown that there is a concurrent gradual disappearance of the acid. In contrast with the situation in living muscle, in which each stimulus sets off a series of linked reactions leading to the production of acid, to its disappearance and to the resynthesis of hexose phosphate, the effect of those chemical or physico-chemical changes which make up the immediate death process is to bring about a production of lactic acid without initiating also the reactions of stages *d* and *e* by which it is promptly removed and the phosphate replaced.

SMOOTH MUSCLE.

Smooth muscle, found characteristically in the walls of the viscera, in the walls of the bloodvessels, in the deeper layers of the skin (the arrector pilæ muscles), and within the eyeballs, presents a simpler and apparently less specialized structure than skeletal muscle. The cell units are smaller (0.2 to 0.3 mm. average length), and the indications of longitudinal striation fainter than in the latter tissue. Ill-defined cross markings have been described by some observers (Tiegs). The grouping of cells is more commonly in sheets or continuous layers than in separate muscle masses.

The chemistry of smooth muscle action has not been so clearly pictured as has that of skeletal muscle. It is assumed that the production of lactic acid is the central chemical feature in smooth, as in skeletal, muscle and that the oxidation of carbohydrates is the fundamental energy-yielding reaction in one as in the other.

In detail of operation, however, the two types of muscle have almost nothing in common. Skeletal muscle, as shown above, remains continuously at rest until stimulated from outside itself. The effect of stimulation is to set in operation a series of linked reactions whereby there is: (1) The very rapid development of relatively great tension in an "all-or-nothing" manner; (2) the prompt release of tension; (3) the restoration of the former state. The maintenance of tension involves rapidly repeated stimulation

and continuous expenditure of energy. Smooth muscle behaves like skeletal in that it responds to stimulation by contraction. The contractions are, however, much slower and more feeble. Mechanical stimulation, particularly sudden stretching, is very effecting in arousing smooth muscle, whereas the same is not very effective as a direct excitant for skeletal muscle. Induction shocks, on the other hand, which are especially good excitants for the latter tissue, are less well adapted to smooth muscle.

Smooth Muscle Tonus.—In its most important characteristics smooth muscle differs completely from skeletal. Thus smooth muscle may contract to a partial extent, this partial contraction being not a matter of full contraction of some cells and no contraction in others, as is the case in similar contractions in skeletal muscle, but partial drawing up of all the cells that are concerned in the action. Having entered into a state of contraction, whether partial or complete, the muscle mass may "set;" that is, it may come to rest in the contracted state and remain so for a long time without expenditure of energy in excess of basic requirements, and so without fatigue. To cause muscle in this state to relax, some form of inhibitory stimulus (page 75) must be brought to bear. In many smooth muscle structures, sphincters and bloodvessel walls for example, the contracted state is normal in the sense that after the muscle has been caused to relax, by inhibitory stimulation, it returns to the contracted state spontaneously upon cessation of the stimulation. This condition, in which there is sustained contraction, apparently without accompanying functional metabolism, is known as smooth muscle *tonus*. Skeletal muscle shows nothing strictly comparable to it (page 691); in cardiac muscle it is present as strikingly as in smooth muscle (page 94).

Tension in Smooth Muscle.—An important feature of smooth muscle is that the *degree of tension* displayed by the muscle cells need not show any direct relationship with the tonus level at which the cells are "set." In the stomach, for example, the size of the stomach cavity is determined by the state of tonus of the musculature of the stomach wall. In extreme tonus the cavity is reduced to its smallest size, and as tonus relaxes it becomes progressively larger. As will be pointed out under Digestion (page 395), an important feature of stomach operation is that "the stomach fits the food." That is, as food is swallowed there is a sufficient relaxation of tonus so that the size of the cavity is adjusted to its contents. The *pressure* of the stomach wall upon whatever is in the cavity depends on the *tension* maintained by the muscle cells. It has been shown that the pressure within the fundic portion may remain nearly uniform over a wide range of increase in size of the cavity, showing that as tonus relaxes the tension in individual cells is adjusted, thus keeping the pressure exerted by the whole organ

constant. There is, of course, a limit to this power of adjustment. When the limit is passed the tension increases rapidly. It may lead to rupture, as sometimes in the crops of overgreedy fowls; in such an organ as the bladder overdistention gives rise to definite and familiar sensations. The tension at any given tonus level may increase through the operation of what are virtually isometric contractions in the smooth muscle cells. An example of this is the sudden tension that may develop in the partially filled bladder in times of nervous excitement. The release of tension through inhibitory stimulation has already been noted (page 93).

The difference in length between extreme relaxation and extreme contraction is many times greater in smooth than in skeletal muscle. In the latter the difference will not exceed 20 per cent or so of the relaxed length. Smooth muscle, on the other hand, may contract to a small fraction of its maximum length. This is strikingly exemplified in the bladder which, when full of urine, is a sac of smooth muscle of about 250 ml. capacity. In this state the individual muscle cells are in nearly maximal extension. When the bladder empties itself its cavity is virtually obliterated; the total surface of the bladder wall is only a fraction of its surface when extended, and the individual cells are correspondingly contracted.

Smooth muscle may perform active contractions and relaxations from any degree of tonus, except the most extreme, as a base line. Under certain circumstances these may follow one another rhythmically over a long period. The fact that in relaxation the muscle returns accurately to its former state of tonus, as well as the absence of fatigue in the maintenance of the latter, has led many physiologists to the belief that tonus depends on an entirely separate mechanism within the cells from that which operates in active contraction. At the present time not enough evidence is available for deciding this question one way or the other.

CARDIAC MUSCLE.

Cardiac muscle is in some respects intermediate between smooth and skeletal. In rapidity and force of action it approximates the latter. In its ability to take a certain state of tonus and to contract and relax from that as a base line it resembles the former. The peculiar property of cardiac muscle tissue is its marked power of *automatic rhythmicity;* that is of rhythmic contraction and relaxation independently of any external stimulation. In the vertebrate heart the cardiac muscular tissue shows an increasing degree of specialization in the direction of augmented *muscular power* as one passes from the venous to the arterial end of the organ. The chambers toward the arterial end beat especially strongly; but

the peculiar cardiac property of automatic rhythmicity is sacrificed to some extent, so that the arterial chambers show a less highly developed automacity than do the less specialized chambers toward the venous end. This fact, as will be pointed out under the head of Circulation (page 292) is of great moment to the proper operation of the heart.

Inorganic Salts in Relation to Cardiac Activity.—It has long been known that automatic rhythmicity is closely dependent on the maintenance of a correct balance among the inorganic salts of cardiac tissue. In fact, the first inkling of the importance of inorganic salts to tissues was had through studies of cardiac rhythmicity by Sidney Ringer, whose work is commemorated in the familiar saline mixture that bears his name. In accordance with our present conception of the cell membrane and its significance, and following the line of thought developed in the analysis of skeletal muscle functioning, we may suggest that in cardiac tissue the recovery processes following contraction lead to the production of a compound equivalent to hexose phosphate, but so unstable that it decomposes spontaneously as soon as a certain quantity has accumulated, provided the cell membrane has the proper degree of permeability; the permeability, in turn, is determined by the proportion of inorganic salts present in the surrounding medium.

Refractory Period.—The synthesis of the unstable compound on which contraction depends goes on comparatively slowly in cardiac tissue, in contrast with the exceedingly rapid synthesis of the corresponding compound in skeletal muscle. The effect of this is that the processes in heart muscle equivalent to those of stage *d* in skeletal, leading to relaxation, always have time to go well on toward completion before enough decomposable compound for another contraction has accumulated. Heart muscle is like skeletal and smooth muscle in being responsive to external stimulation. It cannot respond after a contraction, however, until a certain quantity of decomposable compound has accumulated. Therefore, during and immediately following a contraction there is a period, known as the *refractory period*, in which stimulation has no effect. This is succeeded at once by a brief period in which decomposable substance is accumulating, and in which, therefore, the tissue is becoming increasingly susceptible to excitation. As soon as the normal quantity is regained the automatic property is in position to assert itself, setting off another contraction. Since the height of contraction depends on the amount of decomposable substance present, and not on the strength of stimulation, the heart obeys the "all-or-nothing" law. In fact, this principle was discovered in connection with studies of heart activity. The slowness with which decomposable substance is synthesized makes it impossible to

"tetanize" the heart, since it will always have time to relax during the refractory period, no matter how frequently stimuli are being sent into it.

Conduction of Excitation Over Heart Tissue.—An important feature of cardiac tissue is the existence of free conductivity from cell to cell. In skeletal muscle the sarcolemma acts as a limiting boundary so effectively that while disturbances of equilibrium involve all parts of the stimulated fibers they do not spread to adjoining fibers. In cardiac muscle, on the other hand, the results of an upset of equilibrium, whether this be spontaneous or the effect of stimulation, spread from cell to cell until all the cells that are in continuity are involved. When we recall that skeletal muscle has to function fiber by fiber, in order to achieve the fine gradations of contraction of which it is capable, while the heart functions as a whole organ, the significance of this difference in the relation of one cell of the tissue to another becomes clear.

Summary.

Amœboid movement, characteristic of some protozoa and of amœboid cells in higher organisms, is looked upon as due to changes in surface tension at the external cell surfaces.

Ciliary action, which is due to rhythmic alterations of tension between opposite faces of individual cilia, has not been satisfactorily explained. Important features are the inequality between the force of beat in one direction and the other, and the harmony of action of all the cilia on any given ciliated surface. The two features together make cilia effective organs of propulsion or for the generation of water currents.

In the higher animals active movements are based on the development of tension in muscular tissues. These are skeletal, smooth and cardiac.

The skeletal muscle unit is the *fiber*, consisting of sarcolemma, sarcoplasm and fibrils or sarcostyles. Certain interfaces, either between fibrils and sarcoplasm, or within the fibrils themselves, are looked upon as the immediate seats of tension development.

A working picture of the chemical basis of the contractile process in skeletal muscle is as follows: The resting fiber contains an equilibrium mixture of glycogen, glucose and hexose phosphate. Excitation, by increasing cell membrane permeability, leads to an upset of the equilibrium within the fiber, bringing about an explosive decomposition of hexose phosphate, with production of lactic acid. The extent of decomposition is limited by attainment of a new equilibrium in which hydrogen-ion concentration is thought to be the determining factor. Lactic acid, by virtue of its hydrogen ions, induces tension at the effective interfaces. Temporary

removal of the lactic acid, causing relaxation, is an anaërobic process in which formation of sodium lactate is the main factor. Restoration of the initial equilibrium between glycogen, glucose and hexose phosphate, with attendant final removal of lactate from the system, is accomplished through an oxidation of available fuel, apparently carbohydrate exclusively, yielding sufficient energy for an endothermal reaction by which the lactate is resynthesized to glycogen, wholly or in large part.

Both the chemical and mechanical phases of contraction take place rapidly. The *simple twitch* which results from a single stimulus shows first a latent period of about one-hundredth second, then a contraction occupying about four-hundredths second, followed immediately by a relaxation which takes about five-hundredths second.

Contraction against a constant resistance is called *isotonic;* against a continuously increasing resistance, *isometric.*

Since the *degree of tension* depends on the hydrogen-ion concencentration attained, which is a matter of chemical equilibrium, and thus largely independent of the strength of stimulation, individual muscle fibers operate on an "all-or-nothing" basis. Graduations in force of contraction in muscles are obtained by varying the *number of fibers* that share in the action.

The actual work-yield of muscles depends on several factors. One of importance is the inertia to be overcome in contracting. Up to a certain point the greater the inertia the more efficient the contraction.

Stimulation by a rapid succession of shocks causes *physiological tetanus,* a sustained contraction. The continuous presence of lactic acid at the effective interfaces, assumed to be necessary to sustained contraction, is accounted for by postulating an exceedingly rapid resynthesis of hexose phosphate, following its decomposition, so that each quickly recurring stimulus finds a supply at hand. Since each stimulus also sets in operation the stages tending toward relaxation and restoration, tetanus implies continuous expenditure of energy for maintaining the contracted state.

Muscular fatigue, which is failure to contract to the normal extent on stimulation, is thought to be directly due to the accumulation of sodium lactate within the muscle fibers; this accumulation is assumed to interfere with the decomposition of hexose phosphate, and so with contraction. The accumulation of lactate appears to be due, in turn, to a falling off in the restorative oxidations. These may fail, either through accumulation of products of oxidation (CO_2 chiefly), or through inadequacy of the oxygen supply.

In violent exertion in man sodium lactate may accumulate in the blood and tissues to a total maximum estimated at about 130 gms. This represents the extent to which lactate production may

outstrip recovery oxidation. It is equivalent to an "oxygen debt" of 18 or 19 liters. The body tissues generally (or at least all muscle tissues) carry on an excess recovery oxidation whereby the accumulated lactate is reconverted into glycogen, except such as has meanwhile been eliminated through the kidneys. This recovery process may require an hour or more.

Rigor mortis, which is a persistent contraction that develops immediately following the death of muscle, is thought to be due to the liberation of lactic acid; the disappearance of hexose phosphate seems to be a factor also. In the dead tissue the linked reactions leading to relaxation and restoration do not occur, and the release from rigor is a matter of hours, as contrasted with the fraction of a second required for relaxation in living muscle.

Smooth muscle is thought to show the same fundamental chemical processes as skeletal, namely oxidation of carbohydrate and production of lactic acid. It may contract upon stimulation and relax when stimulation ceases; the contractions are much slower and feebler than in skeletal muscles.

Smooth muscles show the following special properties: (*a*) Tonus, which is the ability to contract partially or fully and to hold the state thus assumed without continuous functional metabolism, and hence without fatigue; (*b*) power to adjust the tension maintained by individual cells in the face of a changing tonus, or, in large measure, independently of the tonus; (*c*) a pronounced difference between contracted and relaxed length; (*d*) the power to respond to inhibitory stimulation by relaxation; (*e*) the power to contract and relax from any state of tonus, except the most pronounced, as a base line.

Cardiac muscle approximates skeletal in force and rapidity of contraction; it resembles smooth in its ability to contract from various degrees of tonus as base lines.

The property of *automatic rhythmicity* characterizes cardiac muscle to an exceptional degree. This property is most pronounced in the less specialized cardiac tissues; in the higher vertebrates these are the tissues in the venous portions of the heart. The property depends on the maintenance of a correct salt balance in the environment.

Heart muscle obeys the "all or nothing" law, indicating that contraction is due to the explosive decomposition of some substance, hexose phosphate or its analogue, which decomposes to a limit set by chemical equilibrium, irrespective of the strength of the stimulus by which the reaction is set off.

The resynthesis of the decomposable compound occurs slowly, in comparison with the analogous synthesis in skeletal muscle. The effect is a demonstrable *refractory period*, during which stimulation has no effect. Since the relaxation processes have time to

get well under way during the refractory period heart muscle cannot be "tetanized."

Under normal conditions there is free conductivity from cell to cell in heart muscle. This ensures coördinated activity throughout any part of the heart in which there is cellular continuity.

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CHAPTER VII.

CONDUCTION.

CONDUCTION AN IMPORTANT PROPERTY OF PROTOPLASM.

In Chapter IV the second of the three types of function of which protoplasm is capable is set down as the reception and transmission of disturbances of equilibrium. The reception of disturbances, in other words stimulation, has already been considered (Chapter V). We have now to examine the means by which disturbances are conducted from one point to another. This property is of utmost importance in the functioning of all animals except a few very lowly groups, such as sponges, since the adjustments of the various parts of the organism to one another, and of the organism as a whole to its environment, are based mainly upon it.

The ability to conduct disturbances is looked upon as a fundamental property of protoplasm. This is equivalent to saying that the organization of protoplasm is such that any upset of equilibrium in any part of it necessarily spreads to other parts. The effect of this in such cells as muscle cells, for example, is that stimulation only has to be applied to some one point, from which point it will spread to bring into action all parts of the cell.

NERVE CELLS AND THE NERVE NET.

In nearly all kinds of animals particular cells serve as means of communication between separated parts of the body. These cells, known as *nerve cells*, are specialized in the direction of efficient conduction, just as muscle cells or gland cells are specialized for active contraction or for the manufacture and outpouring of materials. In many of the lower animals, and in some regions in mammals, notably the alimentary tract and the heart, the nerve cells consist of central nucleated portions which give rise to fine protoplasmic extensions leading out in various directions, and fusing at their tips with similar extensions from other nerve cells, the whole forming a continuous network known commonly as the "nerve net." It is impossible to tell where one cell of the nerve net ends and the adjoining one begins, and for practical purposes they may be looked upon as showing complete protoplasmic continuity. A consequence of this is that disturbances anywhere in the net tend to spread widely through it. In fact, they will spread to all parts except as

their passage is blocked by some means or other. This is an admirable arrangement for controlling structures like the heart or the intestine, which work in mass, but is not well adapted for the stimulation of skeletal muscles, which operate fiber by fiber, and are capable of exceedingly delicate adjustments.

THE NEURON.

An organization which provides for the restriction of conduction to definite paths, and yet at the same time offers a rich choice of paths, is required, as we shall see, for the sort of adjustments that skeletal muscles make. The main nervous system in all the higher animals has this kind of organization. Its unit is a single nerve cell, known as a *neuron* (Fig. 11), which resembles the cells of the net in having a central nucleated "cell body" from which fine protoplasmic processes extend. The chief differences between neurons and cells of the nerve net are three: (*a*) The presence of definite polarity in neurons, the protoplasmic processes making up two groups which spring from opposite ends of the cell body; one of these groups consists, in fact, of a single process, known as the *axon*, which may subdivide at a distance from the cell body, but always springs from it as a single strand of protoplasm; the opposite group is made up, in the typical neuron, of numerous finely branched processes known as *dendrites*; this polarity of structure is associated with a polarity of function, the normal direction of conduction being always toward the cell body in the dendrites and away from it in the axon. (*b*) The much greater length that may be attained by axons than by any of the processes found in the nerve net. (*c*) The interruption of physiological continuity between cell and cell. In respect to this latter point, it should be noted that anatomical contact is made between neurons by an intermingling and pressing together of the dendrites of one with fine protoplasmic branches which make up the terminal portions of the axon in another, these latter forming what is known as the *terminal arborization*. There has been much investigation and discussion among neurologists as to whether the neurons are merely in contact or are actually united by the passage of protoplasmic connections from one to the other. The best histological preparations appear to indicate the latter, yet two distinct types of evidence show clearly that some sort of functional barrier exists between neuron and neuron. For one thing, degeneration (page 115) extends to the extreme axon tips of a neuron in which it occurs, but does not cross to the dendrites with which contact is made. The second line of evidence is one that shows definite differences in conductive property between points of union and all other parts of neurons. The nature of these differences is considered below (page 112). They are of great significance since,

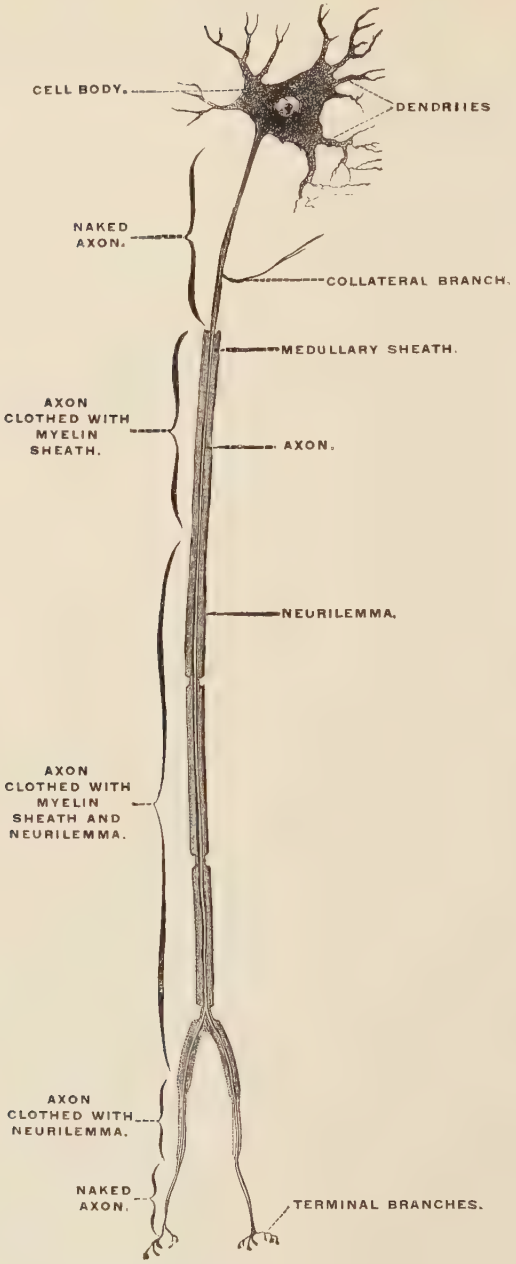

FIG. 11.—Diagram of neuron. (Stöhr.)

as we shall see, the functioning of the nervous system as a whole is determined in large degree by the factors which regulate the passage of disturbances from neuron to neuron. To facilitate description the junction points are called *synapses;* they may conceivably be composed of systems of equilibrium membranes, or have some other physico-chemical character setting them apart from other portions of the neuron; their exact nature is at present unknown.

Junctions Between Nervous and Non-nervous Structures.—In the regulation of bodily functioning through the nervous system there are also to be taken into account unions of neurons with non-nervous protoplasmic structures. It is obvious that there must be

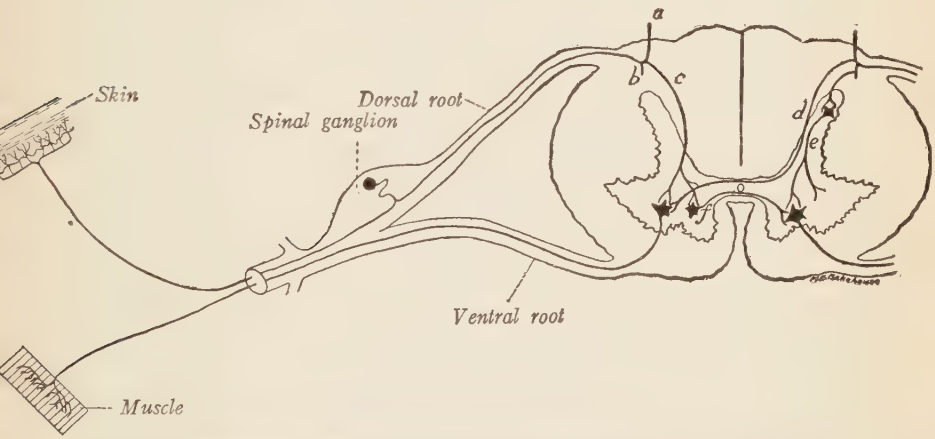

FIG. 12.—Diagrammatic section through the spinal cord and a spinal nerve to illustrate the three main classes of neurons *in situ*. A receptive neuron is shown in the dorsal root, a motor neuron in the ventral and internuncial neurons in the cord itself (*e* and *o*). (From Ranson: Anatomy of the Nervous System, W. B. Saunders Company, Publishers.)

unions with receptor cells (page 76) on one hand, and with the cells of active organs, muscles or glands, on the other. The situations to which the body must adjust itself register themselves by their effects on *receptor* cells; the adjustments are accomplished by means of activities in so-called *effector* organs, consisting of muscle or gland cells, primarily. The transmission of disturbances by which the first series of effects brings the second into play is over paths composed of neurons. It is clear that the cells of the receptor organs must make junction with neurons in forming the starting points of conducting paths, and neurons must make junction, in turn, with muscle or gland cells in forming the terminations of the paths. The nature of these junctions is considered in later chapters (pages 473 and 690). Those between neurons and receptors are

known as *recepto-neural* junctions; between neurons and muscle cells, as *myoneural* junctions.

Receptive, Motor and Internucial Neurons.—In highly organized animals the paths by which connection is made between receptors and effectors are never composed of single neurons, but always of successions of two or more. Neurons that connect with receptor cells are specialized, as indicated in Fig. 12, by having the receiving portion of the neuron represented by a single long axon-like *dendron*, instead of finely branching dendrites. Neurons of this type are known as *afferent* or *receptive* neurons. Their polar character (page 101) is obscured in the adult by a migration during embryonic growth of the two processes, axon and dendron, from the two ends of the cell body to a position side by side, and finally into complete fusion for a distance from the cell body (spinal ganglion cell, Fig. 12). The axon usually divides into two main branches (*a* and *b*, Fig. 12), each of which gives off several or many finer branches, known as *collaterals* (*c*, Fig. 12); these all terminate in the arborizations by which axons always connect with dendrites. Any receptive neuron obviously has as many synaptic connections with neurons in the second rank as it has collaterals. The second rank neurons may terminate directly in effector tissues, in which case they belong to the class of *motor neurons* (ventral root neuron, Fig. 12), or they may be intermediate neurons, forming links in a conducting chain that may include a large number of nerve cells and may bring remote parts of the body into communication. These intermediate cells are known as *internuncial* neurons (*e*, Fig. 12). It should be noted that receptive neurons always communicate at the receiving end with some sort of receptor structure; motor neurons always terminate at their peripheral ends in connection with some active tissue; internuncial neurons are the only type that have synapses at both ends. Receptive neurons can have synapses only at their axon tips; motor neurons only at their dendrite tips.

BASES FOR STUDY OF THE NERVOUS SYSTEM.

To appreciate how adjustments are made through the agency of the nervous system two distinct lines of study must be followed. The first concerns itself with the property of conduction: (*a*) as performed within the limits of single neurons; (*b*) as involving chains of neurons, and so including synapses in the conduction paths. The second takes into account the way in which neurons are disposed in the body, in bringing individual receptors into connection with individual effectors. Both kinds of study are necessary to any sort of understanding of the operation of the nervous system as a whole.

Criteria of Conduction.—To study conduction within neurons, as distinct from conduction involving synapses, resort is had to peripheral nerve trunks, which are bundles of axons or dendrons or both, without cell bodies or synapses. It is comparatively easy to expose a nerve trunk in a recently killed frog or anesthetized mammal and to subject it to electrical stimulation. It is not so easy to determine what happens in the nerve fibers that make up the trunk as the result of conduction within neurons is the result of years of investigation in such stimulation. Such measure of understanding as we now have of which a great variety of means have been used. All that space permits to be given here is a summary of present knowledge, with occasional brief descriptions of the experiments by which the knowledge has been obtained. First of all we must recall that activity within nervous tissues is not attended by any visible changes within the tissues themselves. Even so fundamental a question as whether a given nerve is in action or not must be decided by indirect means. Most peripheral nerve trunks in all kinds of higher animals are mixed, that is to say, they contain axons of motor neurons on their way to connect with muscular tissues and dendrons of receptive neurons leading into the body from receptors in the periphery. Artificial stimulation of such a mixed trunk in an experimental animal presumably excites, or may excite, all the axons and dendrons within the nerve trunk. Positive evidence of such excitation is furnished by the contraction of muscle fibers with which axons in the nerve trunk connect directly. This evidence obviously proves only that some of the *motor* axons have been in action. To obtain evidence of function in the *receptive* dendrons reflexes (page 120) may be evoked or indication of the arousing of sensations may be obtained. In experimental animals under anesthesia sensations obviously cannot be used as criteria; nor are the conditions of the experiment always such that reflexes can be relied on for the purpose. A great step in advance was, therefore, gained when methods were perfected for accurate registration of the delicate "action currents" which accompany all functional activity in nerves, as in other tissues (page 71). There appears to be no doubt that the potential differences causing the "action currents" are fundamentally related to nervous functioning, and therefore are as reliable criteria of nervous action as the contraction of the muscle fibers connected with motor axons. Much of our present knowledge of nervous action has been established by experiments in which the action current has served as the index of activity.

The Local Excitatory Process.—To bring excitation of nerve in line with the picture of protoplasmic excitation in general already given (page 69), we have to look on the effect of stimulation as an increase in permeability in the cell membrane. The axon is a cylindrical thread of protoplasm enclosed, of necessity, within an

equilibrium membrane. The exact relation of the latter to the myelin sheath or the neurilemma cannot be stated, nor is it important for our present discussion that it should be. Stimulation, electrical or otherwise, is pictured as increasing the permeability of the membrane, thus permitting the escape of some positive ions, with a resultant lowering of the electrical potential immediately about the point of stimulation. This constitutes the "local excitatory process." Unless the difference of potential set up by this local process exceeds a certain minimum there is no spread of the disturbance, and the membrane, if left alone, quickly returns to its former state of equilibrium. It is believed that stimuli too weak to produce active response set up "subliminal" local potential differences of this kind. The reason for believing this is that if such stimuli are repeated with sufficient frequency their effects pile up, or *summate*, until an active response is set off. This is taken to mean that the slight changes in the membrane induced by the weak stimuli persist long enough so that following stimuli catch the membrane in a somewhat altered state and add their effects to those that have preceded them, thus by summation bringing about an effective disturbance of equilibrium.

THE NERVE IMPULSE.

Whenever the local excitatory process is of adequate magnitude it sets off in the axon a "propagated disturbance," known commonly as a *nerve impulse*. This is pictured as primarily a more deep-seated upset in equilibrium than the local process that sets it off, and one which spreads rapidly from the point of stimulation to adjoining points on the axon. The necessary result of such an upset of equilibrium as indicated is a shift of the physico-chemical state of the system to a new equilibrium. This second equilibrium must be established in order that the process of shifting can come to an end. It has been shown (Keith Lucas) that in mammalian nerve at ordinary temperatures the second equilibrium is reached in an extraordinarily short time. The interval is measured in thousandths of a second (the unit, one-thousandth second, is called 1 sigma, represented by σ). The actual time depends on the temperature. At 37° C., the temperature of the human body, it is about 1.6 σ. During this shift toward a new equilibrium the nerve is wholly unresponsive to stimulation. This constitutes, then, an *absolute refractory period*, corresponding to the refractory period as seen in the heart (page 95).

The Relative Refractory Phase.—Immediately following the absolute refractory period there is a return toward the former state. This also proceeds rapidly, occupying about 6 or 7 σ at body temperature. The situation is pictured diagrammatically in Fig. 13,

where the curve of altered neuron condition following a single adequate local excitatory process is set down. The phase of restoration is called the *relative refractory period*. The neuron is less sensitive to stimulation during this period than normally, but can be excited if strong enough stimuli are used. The resulting disturbances are not as great as those obtained when the resting nerve is excited. The second equilibrium, which is the state to which the system shifts after every excitation, is presumably the same every time the nerve responds, but the beginning state is less

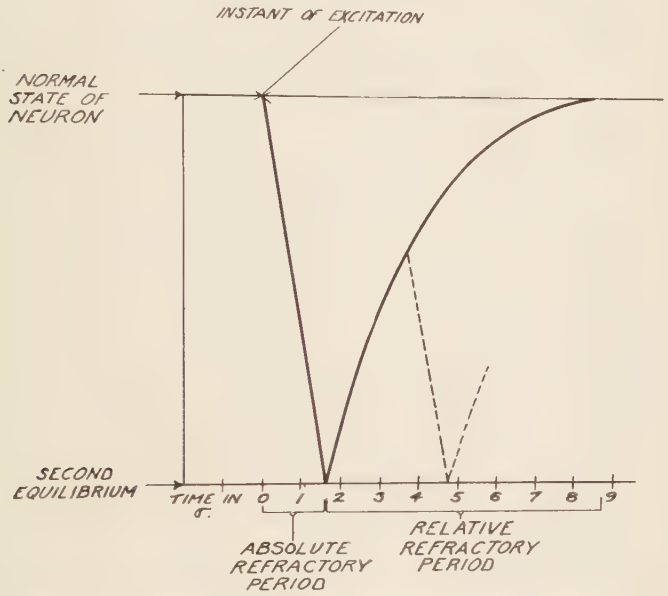

FIG. 13.—Diagram of absolute and relative refractory phases. Dotted line indicates reduced disturbance due to excitation in relative refractory period.

removed from this final state during the relative refractory period, when the nerve is in process of recovery, than in the completely restored condition of the resting nerve. Assuming the size of the disturbance to depend on the amount of shift, it is necessarily less during the relative refractory period than at other times.

FUNCTIONAL METABOLISM IN NERVE TRUNKS.

The change in size of the propagated disturbance discussed above has great significance in the interpretation of nervous functioning in the body at large (page 125), but before pursuing it further some features of the disturbance itself remain to be considered. The

absolute refractory period is pictured above as an instant during which the physico-chemical state of the axon is shifting toward a new equilibrium, and the relative refractory period as the instant during which the former state is being restored. According to the generalized picture of protoplasmic function given in Chapter IV, any exothermal reactions involved in nerve functioning would be expected to occur during the relative refractory period, *i. e.*, in the phase of restoration. The direct criteria of exothermal reactions are, as already noted, increased oxygen consumption, carbon dioxide production, and heat evolution; an indirect criterion is susceptibility to fatigue. The extreme brevity of the absolute and relative refractory periods implies a very slight equilibrium shift underlying the propagated disturbance and a highly efficient restoration process. It is to be expected, therefore, that the direct criteria mentioned above should be on a very small scale if present at all. Various delicate tests for oxygen consumption and carbon dioxide production have been used in the attempt to demonstrate exothermal reactions in nerve functioning. These tests show that axons utilize oxygen and give off carbon dioxide in basic metabolism, agreeing thus with other protoplasmic tissues. They also indicate, although somewhat less surely, that both oxygen consumption and carbon dioxide production are increased during and immediately following the passage of impulses. The amounts of gas involved are minute, being of the order of 3.5×10^{-6} ml. per gram of nerve tissue per minute during rest, and not more than twice the above value during and following active function (see H. Davis for experimental data). The figure for resting nerve is only about two-hundredths of the corresponding figure for oxygen consumption in resting muscle and the relative increase in the active tissue only about one-sixth as great (page 219).

A. V. Hill and co-workers, by a method of extraordinary delicacy, have demonstrated that functioning nerve trunks give off slightly more heat than resting trunks. Thus, all the criteria of oxidative metabolism as a factor in the recovery process in nerve agree in indicating its occurrence, but on an exceedingly minute scale. The escape of CO_2 by dialysis or otherwise evidently keeps pace with its production, as is proved by the fact that nerve axons are non-susceptible to fatigue; a nerve trunk may be stimulated fifty or more times a second for hours without suffering any impairment of its power to conduct; the propagated disturbances maintain full magnitude throughout. The conclusion is that the equilibrium shift which constitutes the propagated disturbance involves an exceedingly small energy change; consequently the restoration of the former equilibrium is accomplished also with minimal energy expenditure.

THE PROPAGATED DISTURBANCE.

The propagated disturbance, as set off by the local excitatory process, is the passage along the axon of the primary equilibrium shift (absolute refractory period) together with the recovery process (relative refractory period). The precise nature of the influence causing the shift of equilibrium at one point to spread to adjacent points is not known. The simplest explanation to suggest itself is that the potential difference attending the equilibrium shift causes a movement of ions between the region in activity and the adjoining inactive region, the movement being of sufficient intensity to upset the equilibrium in the inactive region. Whether ionic movement or some other factor is responsible, each region as it comes into activity passes the effect on to the inactive region adjacent to it. The disturbance at any point has very much the same relation to the adjacent inactive point as the local excitatory process set up by the initial stimulation has to the first point at which the disturbance is established.

A fact of great importance in the detailed analysis of nervous functioning is that different classes of receptive dendrons (presumably dendrons springing from different types of receptors) exist, differentiated from one another by minute but definite differences in the time relations of absolute and relative refractory periods, and also by differences in the speed with which the disturbance progresses along the dendron (see next paragraph). These differences are in all probability important factors in determining the choice of paths followed by particular disturbances over the nervous system as a whole (page 125), although how they operate is not yet known.

VELOCITY OF NERVE IMPULSES.

If the exciting stimulus is applied anywhere except at the extreme tip of the axon or dendron, so that there are portions of the neuron on both sides of the region in which the local excitatory process is set up, a propagated disturbance moves away from the point of stimulation in each direction. The velocity with which it moves depends, presumably, primarily on the physico-chemical state of the neuron; the fact that detectable differences in normal velocity exist (see above) seems to imply corresponding physico-chemical differences among different classes of dendrons. The velocity is also dependent on the temperature, becoming greater as the temperature rises, within physiological limits. The temperature coefficient (page 156) is low, being given by Bayliss as 1.79. At ordinary room temperatures (21° to 26° C.) the average velocity of impulses in motor axons of frogs' nerves is stated at about 40 meters per second

(Erlanger and Gasser); the most quickly moving impulses over dendrons (sensory alpha) have substantially the same velocity. The other classes of sensory impulses (beta, gamma and delta) have an average velocity about one-half as great. In dogs at 38° C. the same observers found velocities of motor and sensory alpha impulses ranging around 70 meters per second. Impulses thought to be sensory delta have been observed in dogs' nerves moving at the relatively slow rate of 12 to 15 meters per second. In non-myelinated nerves in some invertebrates speeds as low as 1 cm. per second have been observed.

Nerve Impulses Obey "All-or-Nothing" Principle.—So long as the condition of the neuron remains normal the progress of the disturbance is not attended by any falling off in its size. This is in accordance with the understanding we have formed of the nature of the disturbance, as a change from an existing to a new equilibrium, and implies throughout the neuron a uniform physico-chemical state at which the disturbance begins, and a uniform equilibrium toward which it shifts. The "all-or-nothing" conception (page 85) thus applies to conduction within neurons, since the size of the disturbance is independent of the magnitude of the exciting stimulus, provided the latter is adequate, being determined rather by the physico-chemical state of the tissue. The nature of the disturbance, including as it does an absolute refractory phase, makes it impossible for nervous conduction to be strictly continuous. Between each disturbance and the next there must be an interval to permit of some degree of recovery. The expression "nerve impulse," used commonly to designate nerve activity, is fortunate in that it brings out this impulsive character in nervous functioning, emphasizing the fact that what we really have is a stream of successive impulses, each separated from its predecessor on account of the refractory period.

Narcosis Reduces the Size of Impulses. — The "all-or-nothing" principle, as applied to nerve trunk conduction, relates the size of the propagated disturbances to the condition of the axons (or dendrons) within which the nerve impulses are occurring. In accordance with this principle we should expect impairment in the condition of the conducting fibers, however brought about, to reduce the size of the disturbances. Impairment can be brought about experimentally by subjecting a nerve trunk to the action of narcotics, such as ether or alcohol. If we suppose a short stretch of a long nerve trunk to be thus treated, and nerve impulses to be started along the trunk in a normal region, these impulses should, in accordance with the "all-or-nothing" principle, continue at full or normal size while they are traversing the normal portion of the trunk, but upon entering the narcotized area should suffer reduction in size, the degree of reduction depending on the depth of narcosis,

and ranging from slight decrease in size to complete extinction. That this actually occurs can be demonstrated by comparing the size of the action current in a normal region with its size in the narcotized area. It will be found that the action current is always reduced in the latter region. The experiment, as just described, is not wholly satisfactory, since in a nerve trunk consisting of numerous fibers reduction in the size of the action current may be due either to a decrease in the magnitude of the disturbance in all the fibers, or to complete extinction of the impulses in some, and their continuance at full intensity in others To prove that there is an actual reduction in magnitude of impulses within a narcotized area it is necessary to determine the state of affairs in a normal portion of nerve *beyond* the narcotized area, that is, on the side away from the region in which impulses were first started. It is clear that if impulses suffer extinction in the narcotized portions of any fibers no impulses will emerge into the normal regions of those fibers beyond the area of narcosis. If, on the other hand, the impulses are merely reduced in intensity, but not extinguished, they should emerge, and furthermore, according to the "all-or-nothing" principle, at once resume full size. This latter is what actually happens, at least in part of the neurons, as proved by the fact that the action current is larger in the stretch of normal nerve beyond the narcotized area than in the area itself.

In this return of the action current to quite or nearly its former size lies the proof, not only of the effect of an area of impairment in reducing the size of propagated disturbances, but of the applicability of the "all-or-nothing" principle to nerve-trunk conduction as well.

Keith Lucas, to whom we are chiefly indebted for the introduction into physiology of the "all-or-nothing" conception in relation to the functioning of skeletal muscle and nerve, held the view that regions of impaired conductivity affect nerve impulses that enter them in such a way as to bring about a continuous decline in the magnitude of the impulses as they pass along the regions of impairment. According to this view impulses fall off more or less gradually during their passage along a region of impaired conductivity, and the question of whether they will or will not be extinguished is determined mainly by the length of the impaired area, the chance of emergence becoming progressively less and less as the length of the area of impaired conductivity increases. This type of conduction was named by Lucas "conduction with decrement," and both he and physiologists generally looked upon it as probably of great significance in nervous functioning, particularly because lessened conductivity appears to be a cardinal property of myoneural and synaptic junctions, and if these junctions conduct with decrement the fact must be taken into account in interpreting the action

of the nervous system. Very recently two groups of observers, Kato and associates and Forbes and colleagues, have shown experimentally that conduction in narcotized nerves does not occur with decrement. Instead of a falling off as the region is penetrated there is an abrupt drop to a constant size which depends on the depth of the narcosis. This finding is more nearly in accord with the physico-chemical situation in nerve as we understand it than is the decrement theory.[1]

Synapses and Myoneural Junctions Regions of Difficult Conduction.—A great deal of study has been devoted to the behavior of narcotized nerve trunks because they constitute regions of impaired, and hence difficult, conduction artificially induced. It is believed that synapses and myoneural junctions are regions in which conduction is naturally more difficult than in other parts of the nervous system, and since, as already pointed out (page 103) the interpretation of the functioning of the nervous system as a whole includes an understanding of the factors which regulate the passage of impulses across synapses, it is clear that any information showing how areas of difficult conduction react may be helpful toward a solution of the larger problem.

SPECIAL PROPERTIES OF SYNAPSES.

We turn now from considering the conduction of impulses within single neurons to a study of transmission over nerve paths, in which synapses have to be passed. Our first task is to note the special properties of these junctions, and then to inquire how these properties affect conduction over the great aggregation of paths of which the nervous system is composed.

Irreversibility.—The peculiarity of conduction involving synapses to be first considered is its *irreversibility*. Nerve impulses may cross synapses from the arborizations in which axons terminate to the dendrites of the neurons with which the axons are in connection, but they cannot cross in the reverse direction. The result of this in a typical nerve path, such as is pictured diagrammatically in Fig. 12, is to make the direction of effective conduction always away from the receptor and toward the effector. An impulse started in any neuron of the path may cross synapses leading toward effectors, but cannot cross any leading toward receptors.

Difficult Conduction.—A second feature of synapses, and in the main of myoneural junctions as well, is that already mentioned

[1] Adrian's experiment with two narcotized areas, widely used as an easily made demonstration of the "all-or-nothing" principle, depends for its validity on conduction with decrement, and in the light of present knowledge cannot be accepted as proving the principle. This is an interesting example of an experiment, not in itself valid, which has been of great service in establishing a principle which is, on the other hand, entirely sound.

of presenting greater difficulty of conduction than characterizes other portions of the neurons. We may borrow from the terminology of electricity and say that these junctional structures offer more resistance to the passage of impulses than do any other portions of the paths. The effect of this increased resistance is to establish a liability, or at least a possibility, that impulses arriving at junction points may be unable to pass, on account of the more difficult conduction, and so may be extinguished. If this fate

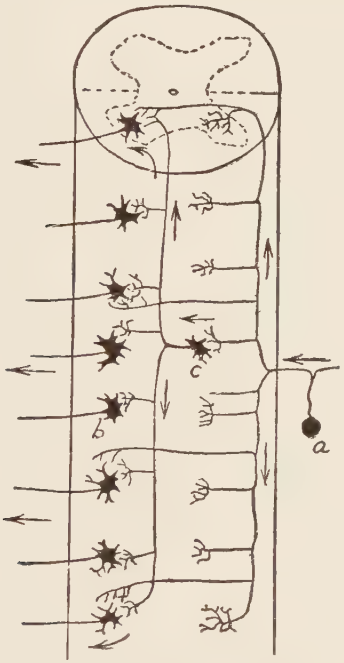

FIG. 14.—Diagram of a portion of the cord, showing numerous possible paths. *a*, a receptive neuron with anterior and posterior terminals and 11 collaterals, offering 13 potential outlets; *c*, an internuncial neuron in synaptic connection with *a* by one of *a*'s collaterals; *c* is shown with eight distinct terminal arborizations; *b*, one of a series of eight motor neurons, all in synaptic connection either with *a* or *c* (Cajal). (From Ranson: Anatomy of the Nervous System, W. B. Saunders Company, Publishers.)

overtakes them there is, of course, an end to conduction so far as the particular paths involved are concerned. When we recall that probably all axons are more or less branched, so that all have more than one outlet, and note, also, that the degree of resistance to conduction may be presumed to be different in the different outlets, we see how this property affords a basis for the selection from among a large number of possible paths of particular ones to be followed by the nerve impulses. The situation is illustrated in Fig. 14,

in which several intercommunicating neurons are shown diagrammatically, and it is seen how the course followed by a nerve impulse may be determined by the different resistances offered by the various synapses.

Decrease in Velocity.—Associated with the property just described is another feature of synaptic function, namely a definite decrease in the velocity of impulses. The time consumed in the passage of impulses from one region of the body to another can often be determined with great accuracy, and it has been shown that when the path of the impulses includes the central nervous system, a region which cannot be traversed for any distance without involving one or more synapses, the time required always exceeds by an easily demonstrated amount that which would be necessary if movement through the central nervous system were at the same velocity as through peripheral nerve trunks. Since the synapses are the only structures peculiar to the central nervous system in which conduction is known to be difficult, it is concluded that the delay in completing the passage is due to a slower rate of movement through them than through the other portions of the path.

Ready Fatigability.—A fourth characteristic of synapses is the relative ease with which they can be fatigued, in contrast with the essential indefatigability of axons. While the passage of prolonged streams of impulses does not affect the ability of nerve trunks to conduct, the persistent bombardment of synapses with impulses in rapid succession quickly affects the junctions so that impulses which formerly passed them successfully are now extinguished.

Susceptibility to Anesthetics and Lack of Oxygen.—Marked susceptibility to anesthetics and to lack of oxygen are other features distinguishing synapses from axons. The latter are, it is true, affected unfavorably by both these agencies, but much less promptly than are synapses. Thus nerve trunks will continue to conduct in substantially normal fashion for a good many minutes after their oxygen supply is cut off, while synapses go out of function very promptly after the same treatment. Similarly, nerve trunks may be narcotized, but only by the application of the anesthetic drug in considerable concentration, while much smaller concentrations suffice to depress synapses to a point such that impulses cannot pass them. In drug anesthesia in human beings the desired degree of narcotization is one that puts certain of the higher synapses in the central nervous system out of function, while leaving all other nervous structures virtually unaffected.

Synapse Properties the Key to Complex Nervous Function.—This summary of the special properties of synapses is of importance since, as already intimated, there is very good reason to believe that the key to the complex functioning of the nervous system as a mechanism for mediating bodily adjustments is to be found in large

part in the way in which synapses operate to regulate the movements of nerve impulses. This view, which was first advanced by Sherrington, and has since been adopted generally by physiologists, has made possible some degree of real progress toward insight into the underlying mechanism of all nervous action, including the highest manifestations of such action in the working of the human brain. In Chapter VIII this matter is developed in some detail. It is desired, before passing to that topic, to give some account of the nutritive situation in the nervous system, including a discussion of the functions of the cell body, this part of the neuron having been neglected thus far.

FUNCTIONS OF THE CELL BODY.

Neurons are derived embryonically from undifferentiated cells in which nucleus and cytoplasm are to all appearance similar in constitution and relationship to corresponding structures in other cells. In the course of development the outgrowing of cytoplasm takes place by which the axon and dendrites are formed. Characteristic structures also appear within the cytoplasm of the cell bodies. The meaning of these latter is at present obscure, particularly in view of the considerable mass of evidence indicating nerve conduction to be primarily a matter of cell-membrane function, and therefore tending to minimize the importance in simple conduction of the structures within the cytoplasm. The nucleus may be supposed to function in nerve cells in the same general way as in other cells. In Chapter II this function is described as concerned with that stage of basic metabolism in which nutritive material is made utilizable for carrying on the exothermal reactions of the protoplasm. That the same conception applies, at least in a general way, to nerve cell nuclei is indicated by the phenomenon of "Wallerian degeneration."

Wallerian Degeneration.—About 1850 Augustus Waller discovered that if a nerve trunk be cut across all axons and dendrons thus separated from their cell bodies undergo a gradual degeneration, comparable in main features to the degeneration that overtakes the cytoplasm of protozoa upon removal of their nuclei. Conductivity persists in the fibers thus cut off until the degenerative processes are well under way, a matter of hours, or even days, in most forms. In myelinated nerves the degeneration also involves the myelin sheath by which each axon is enclosed. This latter degeneration is of a fatty type, and so is easily demonstrated by the use of osmic acid or other fat stains. The degeneration of the cut off portions of the neurons is final. There are also degenerative changes in the parts of the neurons still in connection with the cell bodies, but these are transient, and appear to be due to the upset in general

nutritive equilibrium which follows the sudden cutting off of a portion of the protoplasm of which the cell is composed. Following degeneration (in the peripheral nervous system, but not in the central) there is a regeneration which consists of an outgrowth of each axon or dendron from its stump. These outgrowths follow the course of the former nerve trunk, the guiding influence being clearly chemical, the specific guiding substances probably being materials which remain in the region of the nerve trunk after the degeneration has run its course. This constitutes an interesting example of the phenomenon of chemotaxis (definite response to chemical influence) in so highly organized a form as man.

The phenomenon of degeneration proves that the nucleus is concerned with the nutrition of the entire neuron. How it actually performs its task is difficult to imagine, especially in neurons with very long processes. In such a huge mammal as a whale there are known to be individual neurons whose total length amounts to 10 meters or more, and yet whose diameter and cell-body dimensions are substantially the same as in man. There is no reason to suppose that the dependence of the axon upon the cell body is any different in such neurons than in the smaller units in which degeneration has been actually demonstrated, yet how the influence of the nucleus is brought to bear upon the metabolic processes going on in remote parts of such long neurons we cannot now conceive.

Cell Body Without Special Function in Conduction.—So far as conduction is concerned there is no evidence that the cell body functions in any special way. In fact, in certain crustacea in which the cell bodies of particular groups of receptive neurons are on side branches quite a distance from the main axons, it has been shown that the cell bodies can be cut off entirely without immediately deleterious effect on the transmission of impulses along the axons. In these forms the cell bodies seem not to be in the path of conduction at all, although in typical neurons the path of conduction appears to include the cell bodies as anatomically intermediate between dendrites and axons, but in function precisely similar, not influencing nor modifying in any way the passage of disturbances through them. The ability to modify disturbances is, according to the current view-point, confined strictly to the synapses.

Summary.

Conduction, as a fundamental property of protoplasm, is seen in muscle cells and other types of cells as the means by which stimulation applied at some one point spreads to all parts of the cell.

The *nerve net* represents a primitive stage in the setting aside of specialized cells to serve as means of communication between separated parts of the body. In man this type of structure occurs

in the heart and in the alimentary tract, where mass control is prominent, and sharply localized regulation not in evidence.

The *main nervous system* in all the higher animals is made up of cell units known as *neurons*. Important characteristics of neurons are: (*a*) Polarity; (*b*) possible attainment of great length by the axons; (*c*) the interruption of physiological continuity between cell and cell.

Synapses are points of contact between one neuron and another. They consist of exceedingly fine protoplasmic terminal arborizations at the axon tip of one neuron in union with exceedingly fine dendrites arising from the cell body of another. Current interpretations of the functioning of the nervous system as a whole center largely around the view that conduction across synapses differs from, and is more difficult than, conduction within neurons.

The primary function of neurons is to establish communication between receptors and effectors so that bodily adjustments may be carried on successfully. The nerve paths by which these communications are established never consist in the higher animals of single neurons, but always of chains of two or more. *Receptive* neurons make direct connection with cells of receptor organs; they present the important structural feature of an axon-like *dendron* in place of typical dendrites. *Motor* neurons connect directly with effector cells. Intermediate links in any conducting chain are composed of *internuncial* neurons.

Stimulation of a nerve trunk brings about in each nerve fiber (axon or dendron) a localized process, thought to be an alteration in surface-membrane permeability, attended by a lowering of electrical potential. This is the "local excitatory process." The restoration of the former state is not instantaneous, so that if a single local excitation is inadequate to initiate a transmitted disturbance rapidly succeeding stimulations may *summate* the effect until it becomes adequate.

Whenever the local excitatory process is of sufficient intensity it sets off a *propagated disturbance*. This is looked on as a physicochemical change in the neuron at the point of excitation from its resting state to a new equilibrium, followed immediately by a return to the resting state. The change is attended by a lowering of electrical potential, demonstrable as the "action current." Both the primary change of state and the ensuing restoration spread from the point of excitation over the entire neuron, constituting the *nerve impulse*. It is thought that the lowering of potential accompanying the action may cause sufficient ionic movement to upset the equilibrium in adjacent areas, and so cause spread of the impulse.

During the primary change of state the neuron is unresponsive to stimulation (the *absolute refractory period*, about 1.6 σ in duration at body temperatures). During the restoration period, (the

relative refractory period), which endures about 6 to 7 σ, the nerve fiber may be stimulated by local excitatory processes of sufficient intensity, but the size of the resulting propagated disturbances is always less than when obtained from resting tissue.

The present weight of evidence favors the view that the restoration process in axons, following the passage of propagated disturbances over them, involves oxidative metabolism. Increased gaseous metabolism and heat evolution have been demonstrated to occur, but on an exceedingly minute scale.

Nerve impulses move from the point of stimulation in both directions. The *velocity* of transmission depends primarily on the physico-chemical constitution of the neuron, and secondarily on the temperature. The velocity in frogs' motor axons and "alpha" dendrons at room temperatures is stated to average about 40 m. per second; in the other classes of dendrons (beta, gamma, and delta) about one-half that value. In dogs at 38° C., the average for motor axons and alpha dendrons is given as about 70 m. per second; in other dendrons (delta) rates as low as 12 to 15 m. per second are reported.

The nerve impulse accords with the "all-or-nothing" principle in that its magnitude is determined by the physico-chemical state of the system, and hence is not affected by the strength of the stimulus, provided the latter is adequate.

Proof that the "all-or-nothing" principle applies to nervous conduction is afforded by experiments on nerve trunks in which localized impairment of conductivity, with corresponding reduction in the size of the propagated disturbances, is established by the local application of narcotics.

Recent investigations have shown that in regions of impaired conductivity there is a sharp drop to a constant reduced size of the disturbance, rather than a continuous decline in size as the region of impairment is penetrated. This finding is important in connection with the interpretation of the properties of synapses and myoneural junctions, structures of great significance in the functioning of the nervous system as a whole, and looked on as regions in which conduction is more difficult than in other portions of the neurons.

The following special properties of synapses are considered to be of particular importance in connection with the analysis of the activity of the nervous system: (*a*) *Irreversibility*, by virtue of which nerve impulses can pass synapses from axons to dendrites, but cannot pass in the reverse direction; (*b*) *difficult conduction*, which establishes a liability that impulses may fail to pass some synapses, while succeeding in passing others; (*c*) *lessened velocity of transmission*, from which it follows that nervous activity in regions in which many synapses are traversed takes more time than

would be required in nerve paths of equal length but devoid of these structures; (*d*) *relative susceptibility to fatigue*, in contrast with the essential indefatigability of nerve trunks; (*e*) *marked susceptibility to anesthetics and to lack of oxygen*, properties which cause portions of the nervous system rich in synapses to succumb more quickly to these unfavorable influences than do regions consisting mainly of axons.

In neurons, as in all other kinds of living cells, those phases of metabolism that are immediately concerned with making nutritive materials utilizable are dependent on the nucleus. Cutting off any part of a neuron from the cell body is followed shortly, therefore, by degeneration of the separated part. How the nucleus exercises its function in this respect is not known.

Regeneration is accomplished by an outgrowth of the axon stump. The growing axon follows the former course of the nerve trunk, being directed through chemical influences brought to bear apparently by substances remaining after degeneration has run its course. This is an interesting example of chemotaxis in the higher animals.

There is no evidence that the cell body has any special influence on conduction. The modifications of conduction which occur in connection with bodily adjustments are thought to be accomplished altogether in the synapses.

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CHAPTER VIII.

SIMPLE AND COMPLEX REFLEX ACTION; THE AUTONOMIC NERVOUS SYSTEM.

In Chapter VII the property of conduction, particularly as displayed in nerve tissue, is discussed, and some mention made of the functional relationships that exist among neurons. The purpose of the present chapter is to elaborate this latter theme, in preparation for a detailed study of nervous functioning to which a later section of the book is devoted, and also to furnish the reader with some fundamental data necessary to a ready understanding of much that follows directly.

THE SIMPLE REFLEX.

We have already seen that the nervous system constitutes the means of communication between receptors and effectors, in the carrying out of bodily adjustments. We have also seen that the course followed by nerve impulses in their passage through the nervous system is always in the direction from receptors toward effectors. These two statements lead directly to the further conclusion, which is also borne out by experiment, that nervous activity has its *source*, generally speaking, in the receptors, and its *termination*, also generally speaking, in the effectors. The exceptions to these general statements will be considered in due time, but at present the point to be stressed is that when any nerve path is found to be in action, artificial stimulation being, of course, excluded, we are justified in hunting for some receptor or group of receptors as the place of origin of the impulses that are passing, and for some effector or group of effectors as the destination toward which the impulses are traveling. The basic act of conduction in any higher animal consists of the passage of an impulse or simple stream of impulses from some receptor over the nervous system to some effector. The action as a whole, *i. e.*, stimulation of receptor, passage of impulse stream over a nerve path, and response of effector, is known as a *simple reflex*. The path through the nervous system is commonly referred to as the *reflex arc*, although the expression *reflex path* serves as well.

Central and Peripheral Nervous Systems.—It has already been pointed out that the organization of the nervous system is such as

to make the simplest possible reflex arc consist of two neurons, one receptive or "sensory" and one motor. The connection between the two is by means of a synapse. In man, as in all vertebrates, the nervous system as a whole subdivides into two chief portions, designated respectively as the central and peripheral nervous systems. Both receptors and effectors are located, in the main, in the outlying parts of the body; from these regions connection is made with the central nervous system by means of nerve trunks, 43 pairs in man, 12 cranial and 31 spinal. These trunks are composed chiefly of the axons of motor nerves, and the dendrons of receptive nerves. The spinal nerve trunks are mixed, containing both sorts of fibers; some of the cranial nerves are purely motor, others, purely receptive, and still others mixed like the spinal nerves.

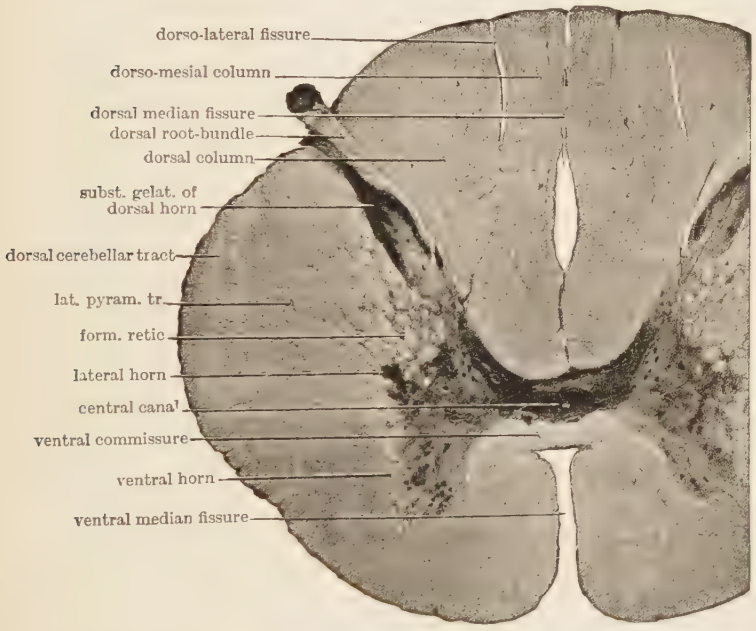

FIG. 15.—Section of human spinal cord from upper cervical region. Photograph. (Magnified about 8 diameters.) (From Schäfer's Essentials of Histology by permission of the author.)

The Spinal Cord. - The central nervous system consists of brain and spinal cord. Within it are all the synapses of the body, except a set belonging to the autonomic system, to be described later. The spinal cord has a much simpler structure than the brain, and therefore serves better for a first account of reflex action. The relation of the spinal nerves to the cord is illustrated diagram-

matically in Fig. 12. As that figure shows, receptive axons enter the cord by a dorsal root and pass to the posterior funiculus; here each divides into ascending and descending portions (*a* and *b*), and extends for a greater or less distance, giving off collaterals at various levels (Fig. 14). Each collateral leaves the posterior funiculus to plunge into the central column of gray matter in which all the synapses of the cord lie (Fig. 15). It should be noted that the gray color of the central column is due to the absence of myelin, the axons losing their sheaths near their tips, and the dendrites and cell bodies being devoid of myelin in the cord as elsewhere in the body.

The receptive neurons make synaptic connection, possibly sometimes directly, but usually through one or more internuncial neurons, with motor neurons. The dendrites and cell bodies of such of the latter as arise within the cord are in the ventral gray horns (Fig. 15). Thence the motor axons extend by way of the ventral roots to the spinal nerves, and so to their connection with effectors in the periphery.

Every Receptive Neuron has Structural Connection with Every Motor Neuron.—The total number of receptive neurons entering the cord, of motor neurons leaving it, and of internuncial neurons making connections within it is very great. Furthermore, each receptive neuron has, as already pointed out, many branches, most of which establish synaptic connection with internuncial neurons, which are in turn richly branched, and in turn have most of their connections with other internuncial neurons. Thus the possible paths which incoming impulses may take increase in number in geometrical progression as we pass successive ranks of neurons. To every part of the central nervous system, both spinal cord and brain, the ramifying paths penetrate. The outgoing paths from cord and brain consist of somatic motor neurons chiefly (the autonomic pathways will be dealt with later). These motor neurons have their dendrites, as already noted, in the anterior columns of gray matter in the cord, and in corresponding regions in the brain. Upon these dendrites converge axon branches from the internuncial, and perhaps receptive, neurons which lie at corresponding levels, each motor neuron being in direct synaptic connection with several internuncial neurons, and perhaps with one or more receptive neurons as well. The interconnections are so extensive that one is justified in declaring every receptive neuron to be in structural communication, directly or indirectly, with every motor neuron. Whether all the possible connections are actually ever made use of is, of course, another matter, in which synaptic resistance is closely concerned. Our present task is to inquire how, in the face of this multiplicity of potential pathways, the course of reflex action is actually guided so that successful bodily adjustment is attained.

Features of Simple Reflex Action.—Examples of simple reflex action are familiar to us all. The standard example is the jerking of the hand away when one inadvertently touches something hot. Coughing and sneezing are other instances, although in these reflexes the nerve paths involved and the resultant muscular action are more complicated than in the simple arm flexion which is the useful response in the first case given. A frog deprived of its brain will live for a long time if kept cool and moist, and in such a preparation many simple reflexes can be evoked by suitable sensory stimulation. General features shared by all of them are: (*a*) An evident tendency for the response to be *serviceable;* thus pinching one toe is followed by withdrawal of the corresponding leg; placing a bit of acidified paper on the flank results in coördinated stroking movements which will presently dislodge the irritating object. (*b*) A clearly *automatic character* in the reactions; repeated application of a certain stimulus, provided fatigue is guarded against, regularly evokes precisely the same response at every repetition, and this is true, in general, not only for successive stimulations within a few minutes, but for the whole lifetime of the animal, and for all animals of the same type of nervous organization; one can predict with great confidence what reactions will follow certain stimulations, provided previous study has shown what to expect. (*c*) A definite *correlation* between the *intensity of stimulation* and the *extent of involvement* of effector units in the response; a weak stimulus regularly arouses a minimal amount of muscular action; stronger and stronger stimuli bring more and more muscles into play; in all this "spreading of reflexes," however, the serviceable character of the reaction is not lost; the effort at adjustment merely becomes more pronounced, amounting in extreme cases to violent struggling on the part of the unconscious experimental animal. (*d*) The *time* elapsing between stimulation and response is *no greater* than is necessary for the passage of nerve impulses over the lengths of axon and across the number of synapses that intervene between the receptors in which the reflex originates and the effectors in which it culminates.

The Theory of Preferred Paths.—To form an acceptable picture of simple reflex action we have to show how impulses passing, in accordance with the "all-or-nothing" principle, over the nervous system with its wealth of intercommunications, can bring about responses that are *serviceable,* that are *automatic,* and that are also *graded* to correspond with the intensity of the exciting stimulation. In respect to the serviceability of the responses we have to recognize that for every receptor or allied group of receptors there is some effector or group of effectors whose activity gives the response that answers the description. In an experimental frog, for example, the flexor muscles of the right leg give the serviceable response to pinching the right toe; the corresponding muscles of the left leg

react suitably when the left toe is pinched. In man a complex group of muscles of expiration produces a useful response to the throat irritation on which the coughing reflex is based. The nervous mechanism must operate in such manner that impulses arising in any given receptor or receptor group find directly open for their passage, out of the multiplicity of possible paths, only that particular one which leads to effectors that will give a suitable response. Since the action is automatic the arrangement by which certain pathways are thus open must be inherent in the organization of the nervous system, so that whenever any given receptor happens to be stimulated the proper course to the suitable effector will be followed inevitably. (Note that inhibitory action from the brain may interrupt reflex paths, and so seemingly afford exceptions to the above statement; see page 730.)

The original suggestion as a means of accounting for this existence of "preferred paths," as advanced by Sherrington, was that the receptive neuron leading from any receptor would always have one particular synapse of less resistance than any of its others, so that an impulse coming from the receptor would find one outlet easier to pass than any other. This would cause the impulse to enter a definite internuncial neuron which, in turn, would have one synapse of less resistance than the others, and so the course of the impulse into the third rank would be determined. The idea can, of course, be extended indefinitely. In due time, perhaps as early as the second rank in some cases, the synapse of least resistance would open into a motor neuron, which would always be the one connecting with the most serviceable effector.

Consequences of the "All-or-Nothing" Principle.—The above scheme of Sherrington's for accounting for paths of least resistance was proposed before the "all-or-nothing" principle with its implications had been recognized as applying to nerve physiology. There is nothing in the principle to invalidate the explanation so long as it is confined to simple paths of least resistance. Difficulties arise, however, when attempts are made to account for the more complex actions of which the nervous system is capable. Each receptive and internuncial neuron has numerous synaptic outlets. According to the Sherrington suggestion one of these outlets in each neuron has less resistance than any of the others. In terms of the "all-or-nothing" principle any nerve impulse started along a neuron spreads with full size to all parts of it, and so tends to have equal magnitude upon its arrival at all the synapses. If all of these but one have too great resistance for a full-sized impulse to pass there would seem, at first thought, no physiological justification for the existence of more than one synaptic outlet from any neuron, since none but the one of least resistance would apparently be passable under any circumstances, there being no means of making full-sized

impulses any larger. The whole scheme of indefinitely rich intercommunication, bases on abundant branching of neurons, would thus seem to be of no avail.

Effects of Strychnine.—There is, however, in addition to the histological evidence of rich neuron branching, experimental proof of the reality of abundant intercommunication throughout the nervous system. An animal, such as a frog, a cat, or even a man, poisoned with strychnine in less than lethal dose, falls into a condition in which sensory stimuli started in any part of the body spread to all parts of the nervous system, so that all the skeletal muscles are excited to strong contraction. There is complete disappearance of "preferred paths;" any sensory stimulus whatever causes a severe convulsion. To explain this it is necessary to suppose that strychnine abolishes all differences in synaptic resistance, making actual the potential connection of each receptor with all the effectors, and proving incidentally that the many branches known to be possessed by receptive and internuncial neurons may function under certain conditions, even though most of them do offer, normally, greater resistance to the passage of impulses than does the one synapse opening into the "preferred" path.

Possible Factors in Determining Complex Reflex Paths.—Various theories have been proposed to explain the automatic selection of serviceable paths when "spreading of reflexes" occurs. It must be admitted that as yet these are in the speculative stage for the most part, and detailed discussion of any of them is unwarranted in a book of the present scope. Some factors which appear likely to be involved may, however, be indicated briefly. A fact of probable significance is that in the normal functioning of the body nerve impulses rarely or never occur singly. The typical nervous discharge is in the form of an *impulse stream;* it is doubtful whether any receptor can be stimulated so briefly as to give rise to only one impulse, except perhaps under very precise experimental conditions, and the evidence is conclusive that nervous discharges of other origins than directly from receptors (page 131) consist of impulse streams. The advantages of an impulse stream over a single impulse are conceivably several. For one thing successive impulses may follow one another at various intervals. If the interval is so short that each impulse after the first falls within the relative refractory period of its predecessor (page 107) the magnitude of all except the first is cut down, and more the earlier in the period the impulses come. Several investigators have suggested that differences in timing within the relative refractory period may account for the failure or success of particular impulse streams in passing given synapses. Associated with the above factor is the finding (Lucas, later modified by Adrian), that under certain con-

ditions of hydrogen-ion concentration, conditions presumably realized within the central nervous system, the relative refractory period may be followed by a period in which the condition of the nerve fiber overshoots that of normal rest, the neuron being for a few sigma at the end of the relative refractory period in such a state that if excited then the resulting disturbance will be larger than otherwise. By postulating a timing of successive impulses such that each falls in this "supernormal phase" of its predecessor a means can be imagined by which synapses not normally passable can be traversed.

Another factor which may possibly play a part in the opening of synapses too resistant to be passed ordinarily is that of *temporal summation.* This is conceived as a change in some synapses as the result of their bombardment by impulses, so that their resistance is reduced. By postulating that the degree of reduction in resistance varies with the interval at which the impulses arrive a basis can be worked out for considerable selection among the various synapses of a given neuron.

Still another factor is brought into play by the *multiple character of many reflex paths.* Strong stimulation nearly always excites more receptors than does weak stimulation. This obviously means the throwing into action of more receptive neurons. Each of these presumably forms the first element in a "preferred" path, which by itself would elicit a definite, but restricted reflex response. As a part of a larger conducting mechanism each contributes its stream of impulses to the whole current of disturbance set up by the strong stimulation. The serviceable response to any strong stimulation is in part the same as to a corresponding weak stimulus; it calls into action all the effectors aroused by the weak stimulation, and some more besides. The reflex path as a whole includes several neurons in each rank. This fact has suggested the possibility that there may be intercommunication among the neurons which make up given ranks, permitting passing back and forth of impulses from neuron to neuron, so that what is happening in one arc may influence what happens in another. The analogy is with a system of parallel roads, intercommunicating by frequent laterals, and each laden with a burden of traffic. As vehicles cross over from one road to another in search of better driving conditions they change the traffic density both in the road left and in the one entered. The effect at the destination, as measured by the arrival of vehicles, depends largely on the distribution of traffic among the various roads. In remotely similar fashion one can picture the reflex effect of strong sensory stimulation as influenced in some degree by the distribution of impulses among the various neurons of each rank in the reflex path as a whole.

COMPLEX REFLEXES.

Reflexes as they occur in the body include both the simple type just described, in which stimulation of one receptor, or at the most of a group of closely related receptors, brings about response of a definite group of effectors, and also others in which the sensory basis is complex, consisting of the simultaneous stimulation of many receptive structures. It is clear that in the complex environment in which men and animals live behavior, to be serviceable, must as often as not be adjusted to situations in which there are many factors at work, and in which, therefore, stimulation is brought to bear on the body through many channels. In any such case streams of sensory impulses will pour into the central nervous system from various parts of the periphery. Impulses moving in this direction are known as *afferent, i. e., toward* the center. These afferent streams are to be translated into outgoing impulse streams (known as *efferent,* because moving *from* the center).

The serviceable muscular response to these multiple afferent impulse streams may or may not be more complex than some that have a more simple sensory basis. For example, the reflex of coughing is usually initiated by irritation of a restricted area in the throat, and hence cannot depend on the stimulation of very many receptors, yet the muscular response is highly complex. In contrast one may note that so simple an act as lifting food from plate to mouth may have behind it stimuli of sight, smell, muscle sense, and of the hunger sense, all giving rise to afferent impulses pouring into the central nervous system, and yet finding expression in the comparatively restricted stream of efferent impulses by which the arm movements are evoked.

The point to be stressed is that while both the "stimulus pattern" on which the reflex is based and the "muscle pattern" involved in the response may have any degree of complexity over a wide range the feature of serviceability tends always to characterize the action. The streams of afferent impulses may have many and diverse sources or few and restricted; the organization of the central nervous system is such that in either event the stream is caused to converge into a narrow efferent path or to spread out into a broad one according to the adaptive requirements of the particular situation prevailing at the moment.

These fundamental features of reflex action are presented at this point so that the reader may have them in mind in connection with the study of various bodily processes in which reflexes enter importantly. For a more extensive presentation of central nervous functioning see page 699 and following pages. There remains for consideration a group of reflexes in which the *efferent* portion of the paths is confined to the *autonomic* subdivision of the nervous

system. These are reflexes in which the effector tissues are either smooth muscles, heart muscle, or glands. On account of the important roles played by these tissues in bodily maintenance an account of their reflex control must be given before the general subject of maintenance comes up for discussion. (The well-being of the organism depends largely on proper operation of the alimentary tract, the heart and bloodvessels, the kidneys, and various glands.)

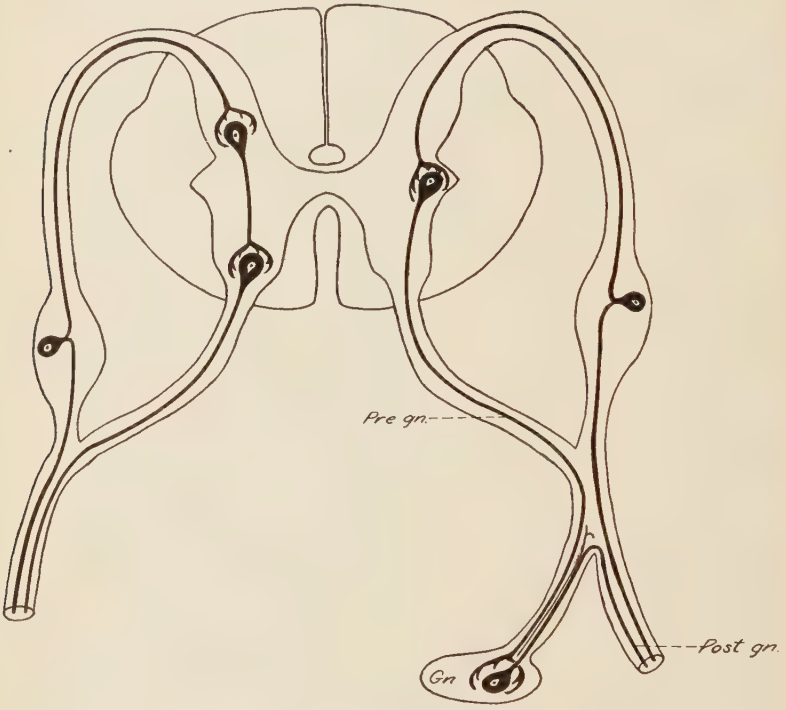

FIG. 16.—Diagram to illustrate the difference between a somatic reflex path (left) and an autonomic (right). The preganglionic fiber, *Pre-gn*, is shown extending through the white ramus to the sympathetic ganglion, *Gn*. The postganglionic fiber, *Post-gn*, is shown returning from the ganglion to the spinal nerve in the gray ramus. (From Gaskell.)

THE AUTONOMIC SYSTEM.

This is the motor innervation of all smooth muscles and of all glands, so far as the latter are under nervous influence. It is analogous in function to the entire series of somatic motor neurons. These latter form the efferent connection between the central nervous system (brain stem and spinal cord) and the skeletal muscles; the autonomic system is the efferent connection between the central system and the smooth muscles and glands. Its special anatomical characteristic is that each path from the brain or cord to a particular effector structure consists of a sequence of two

neurons, instead of being a single neuron, as in the skeletal muscle innervation. The junctions between first and second neurons in all cases are by synapses, corresponding in main features, so far as can be judged, with those already described (page 112), although possessed of certain peculiarities specific to themselves (see page 299). All synapses of the autonomic system are outside the central nervous system, a fact that follows from their position as junction points in paths extending from the central nervous system to the periphery. The synapses are located, along with the cell bodies of the second rank autonomic neurons, in *sympathetic* or *parasympathetic ganglia*. The neurons that extend from the central nervous system to the ganglia (first rank neurons) are called *preganglionic;* they are typically myelinated. Those extending from ganglia to effectors (second rank neurons) are *postganglionic*, and are usually unmyelinated (the gray rami consist of these; see Fig. 16). Preganglionic neurons are in general richly branched, each making synaptic connection with several or many postganglionic neurons. The latter are also typically much branched, each innervating a number of cells of the particular effector tissue to which it extends. The arrangement is looked on as a means of distributing the influence of single preganglionic neurons to a wide group of individual effectors. This distribution corresponds with the fact that the types of effectors having autonomic innervation operate in the main in masses rather than in sharply localized units as do the skeletal muscles (page 101). The arrangement may be looked on as a means of controlling the mass activities of these effectors with an economy of discharge from the central nervous system.

Sympathetic and Parasympathetic Systems. - Preganglionic neurons spring from the central nervous system in three great groups, designated from their regions of origin as the cranial, thoracico-lumbar, and sacral groups respectively. The thoracico-lumbar outflow constitutes the *sympathetic* nervous system of classical anatomy. The cranial and sacral outflows together make up the *parasympathetic* system.

Double Autonomic Innervation. — A feature of smooth muscle already mentioned (page 93) is that it may require stimulation both to excite and to inhibit, namely, to arouse activity on the one hand, and to bring to an end activity already in progress on the other. In general such structures as are susceptible both to excitation and to inhibition have double innervation. Each effector unit makes contact with terminal branches from two postganglionic neurons. An important feature of this double innervation is that it springs typically from distinct subdivisions of the autonomic system. One portion is sympathetic, the other parasympathetic. If the sympathetic innervation is excitatory the parasympathetic is as a rule inhibitory, and *vice versa*. Note that this does not imply one section

of the autonomic system to be always excitatory and the other inhibitory. For some structures the sympathetic system is excitatory for others inhibitory. Whichever action the sympathetic system has the parasympathetic system will usually be found to have the opposite.

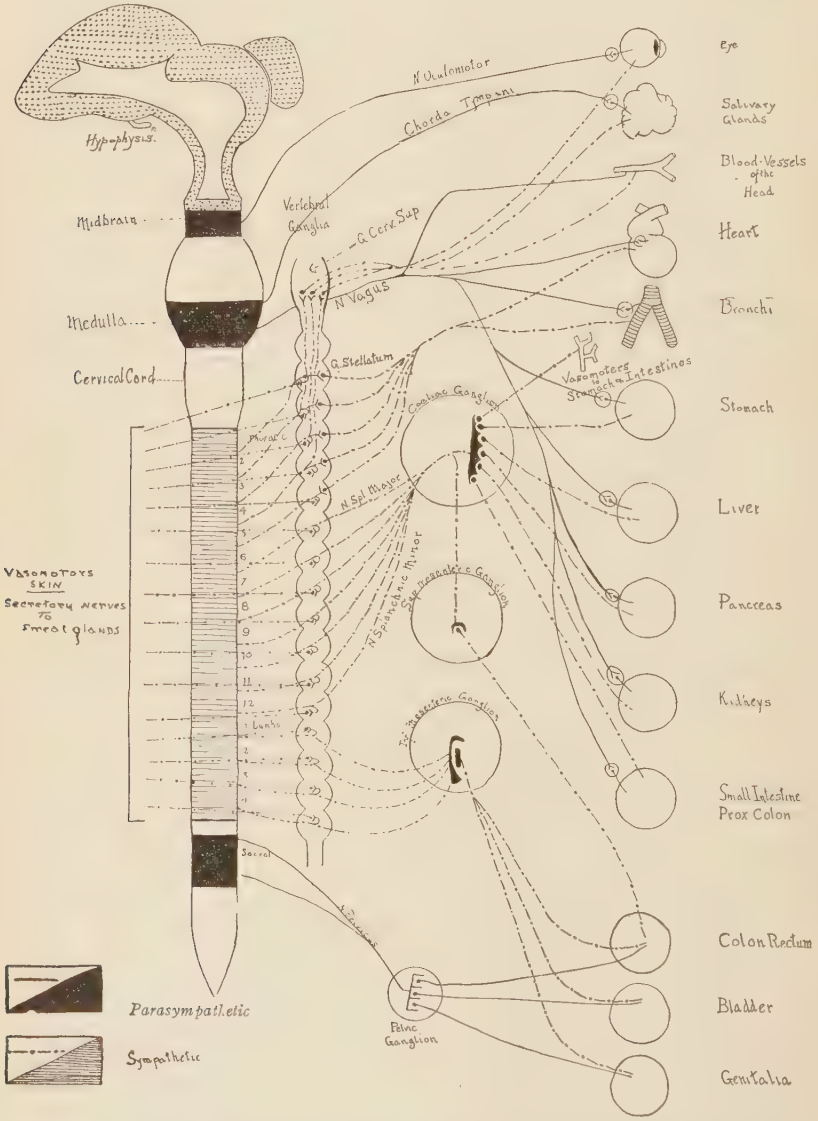

FIG. 17.—Distribution of the various divisions of the autonomic system. Sympathetic fibers are indicated by dotted lines; parasympathetic by unbroken lines. (Kraus, modified from Meyer and Gottlieb, Jour. Nerv. and Ment. Dis., 1918.)

Summary of Autonomic Innervation. - In the accompanying table the principal structures innervated through the autonomic system are listed, together with the nature of the influence, whether excitatory or inhibitory.

Tissue.	Sympathetic.	Parasympathetic.
Arrector pilæ muscles	Excitatory	
Ciliary muscles	....	Excitatory
Sphincter pupillæ	....	Excitatory
Dilator pupillæ	Excitatory	
Salivary glands	Inhibitory	Excitatory
Bronchial muscles	Inhibitory	Excitatory
Heart	Excitatory	Inhibitory
Small bloodvessels	Excitatory (vasoconstriction)	Inhibitory (vasodilatation)
Muscles of alimentary tract (except sphincters)	Inhibitory	Excitatory
Sphincters	Excitatory	Inhibitory
Gastric glands	Inhibitory	Excitatory
Pancreas	?	Excitatory
Liver	Excitatory (mobilization of sugar, p. 178)	
Adrenal medulla	Excitatory	
Muscles of ureters	Inhibitory	Excitatory
	Excitatory ? (p. 441)	
Bladder	Causes tension increase (p. 442)	Excitatory
Sphincter of bladder	....	Inhibitory
Ischio- and bulbo-cavernosus muscles	....	Excitatory
Sweat glands	Excitatory	

Autonomic "Centers." To a large extent the activity of the autonomic system depends on so-called *centers* located chiefly within the medulla, although some subsidiary centers exist in the spinal cord. From these centers streams of nerve impulses proceed, regulating the rate and force of the heart-beat, the blood-pressure, the secretion of sweat, various activities of the alimentary tract, and a number of other bodily processes. All these have much to do with the functioning of the body from moment to moment, and are commonly described as "vital" processes. The centers regulating them are known as "vital" centers.

Autonomic Centers Subject to Both Reflex and Humoral Influence. - The autonomic system is an efferent system. In common with the other great efferent system of the body, *i. e.*, the system of motor nerves to the skeletal muscles, it depends for its activity largely on influences brought in to it by way of afferent nerves from the receptors. In other words, it operates reflexly. Since centers are involved in this reflex action we must suppose streams of afferent impulses to play upon the centers, and to be translated within them into streams of suitably coördinated efferent impulses, which pass promptly to their destinations over the autonomic system. There is, however, more to the operation of most autonomic centers than the simple conversion of afferent into efferent impulse streams. Many of them appear capable of discharging impulses automatically.

Whether this is a true automaticity or is due to chemical excitation brought to the cells of the center by the blood flowing through its vessels is not certain. There are, however, various centers known to be subject to excitation through the blood. Influences thus manifested are designated as *humoral*, to identify them with a source in the blood. Certain centers are susceptible to changes in blood temperature; in this case the humoral influence is physical in nature (see for example, page 447). Some centers react to changes in hydrogen-ion concentration (page 374). Further details concerning the functioning of individual centers will be found in connection with the accounts of the bodily processes with which they are specially concerned.

Summary.

A *simple reflex* is the basic act on which nervous function hinges. It includes stimulation of a *receptor*, passage of nerve impulses over a *reflex arc*, and resulting activity on the part of an *effector*.

Receptors and effectors are in the peripheral parts of the body. They are in communication with the *central nervous system* by means of nerve trunks which make up the *peripheral nervous system*.

All synapses of the body are within the central nervous system, consisting of *brain* and *spinal cord*, except some belonging to the autonomic system.

The richness of branching and of interconnection of neurons is such that each receptor has potential connection with each effector in the body. These potential connections can be made actual by strychnine poisoning.

In operation simple reflexes show the following characteristics among others: (*a*) Serviceableness; (*b*) an automatic nature; (*c*) correlation between intensity of stimulation and extensiveness of response; (*d*) promptness of response.

Sherrington has postulated "paths of least resistance" as a means of accounting for the characteristics of simple reflexes. These are pictured as blocked out by the presence of just one synapse on each neuron with low enough resistance to be traversed by ordinary impulses. The distribution of these synapses of least resistance is taken to be always such as to cause the impulse to pass to the most serviceable effector in relation to the receptor of origin.

The "spreading of reflexes" can be explained in accordance with the "all-or-nothing" principle only by picturing means whereby synapses not ordinarily penetrable by full-sized impulses may become so under certain conditions. The suggested means take advantage of the fact that normal nervous functioning depends on *streams of impulses*, rather than on single impulses. Possible factors of importance are: (*a*) The timing of successive impulses so that

all after the first shall fall in the "supernormal phase" of their predecessors; (*b*) *temporal summation*, *i. e.*, the overcoming of synaptic resistance by bombarding the synapses with streams of properly timed impulses; (*c*) the fact that strong stimulation usually arouses more receptors than does weak, and so calls a series of parallel reflex paths into operation simultaneously.

In the actual functioning of the nervous system *afferent*, *i. e.*, incoming, impulse streams, whether simple or complex, are translated into *efferent*, *i. e.*, outgoing, impulse streams, so organized as to evoke serviceable responses, whether these latter are simple or complex. The serviceable and automatic character of reflex action persists, even though the nervous activity involved is highly complicated.

Smooth and cardiac muscle and gland tissue receive motor innervation through the *autonomic system*. This is the efferent connection for these tissues from the spinal cord. Each path consists of a sequence of two neurons, connected by a synapse.

The synapses of the autonomic system and the cell bodies of the second-rank neurons are located in *ganglia* which lie outside the central nervous system. The neurons which connect the spinal cord with the ganglia are known as *preganglionic;* those that connect the ganglia with the effector cells are called *postganglionic*.

Both pre- and postganglionic neurons are richly branched. The effect of this is to give each preganglionic neuron control over a large group of effector cells.

The autonomic outflows are from three regions of the cord. The *thoracico-lumbar* outflow constitutes the *sympathetic* system of classical anatomy. The *cranial* and *sacral* outflows together make up the *parasympathetic* system.

Such effectors of this group as have both excitatory and inhibitory innervation typically receive the neurons by which the opposing effects are mediated from different subdivisions of the autonomic system.

The activity of the autonomic system is largely regulated by *centers*; these are located chiefly in the medulla. The centers are largely reflex in operation; that is, they translate afferent impulse streams immediately into suitably coördinated efferent streams. In addition to this reflex property some centers are influenced by such factors as blood temperature on the chemical or physico-chemical constitution of their liquid environment. Certain centers appear to be automatic in that they discharge impulses in the absence of recognizable external cause.

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The Autonomic Nervous System. Gaskell: The Involuntary Nervous System, London, 1916.

CHAPTER IX.

GLAND FUNCTION: THE MANUFACTURE AND OUT-POURING OF MATERIAL.

Gland Activity Important in Bodily Functioning.—In Chapter IV the third type of functional metabolism listed is that which forms the heading of this chapter, namely the manufacture and out-pouring of material. We have already seen that in connection with the ordinary metabolism of most kinds of cells, both plant and animal, there are likely to be products of metabolism which are waste products from the standpoint of the cells that produce them, to be eliminated in order that the cells may continue to live and function. In a sense one might look upon the substances produced and given out by gland cells as of this sort. This view, however, falls short of giving a true picture of the relation of gland cells to the body as a whole. As truly as muscle cells are specialized to develop tension, and nerve cells to transmit disturbances, gland cells are specialized to synthesize particular substances and to pass them out for use in other parts of the body. A strict adherence to this description of gland function would require us to list sweat glands and the kidneys under a separate category, since they serve primarily to pass outside themselves matter which enters them from the blood, rather than to manufacture material (pages 142 and 147). But in general they function so much as do other glands that it is convenient to include them in the present discussion.

External and Internal Secretion.—Glands fall into two main groups according to whether they pour their products into surfaces, like the lining of the alimentary tract or of the bladder, that communicate with the outside of the body, or pour them into the blood stream. The former group, or first type, are the glands of *external secretion*, familiarly exemplified in the salivary and sweat glands. Many glands of this type communicate with the regions for which their secretions are destined by means of ducts. The second group includes the so-called ductless glands, or glands of *internal secretion;* the reason for these names is obvious. The physical conditions under which the secretions are poured out differ widely for the two types of glands; they are accordingly dealt with separately.

Structure of a Typical First-type Gland.—A representative gland of the first type consists essentially of a single layer of cells exposed on one surface to the tissue fluid, and indirectly to the blood, sup-

ported on this side by the *basement membrane*, and facing on the opposite surface on the cavity or *lumen* of the gland duct. In many glands economy of space is afforded by an arrangement of the cells in cylindreal or roughly spherical *acini* or *alveoli*, about one layer of cells deep; the outer surface of the cylinder or sphere (but the *inner faces* of the cells) fronts on the tissue fluids; the central cavity of the acinus, on which the *outer faces* of the cells have exposure, communicates with the lumen of the duct.

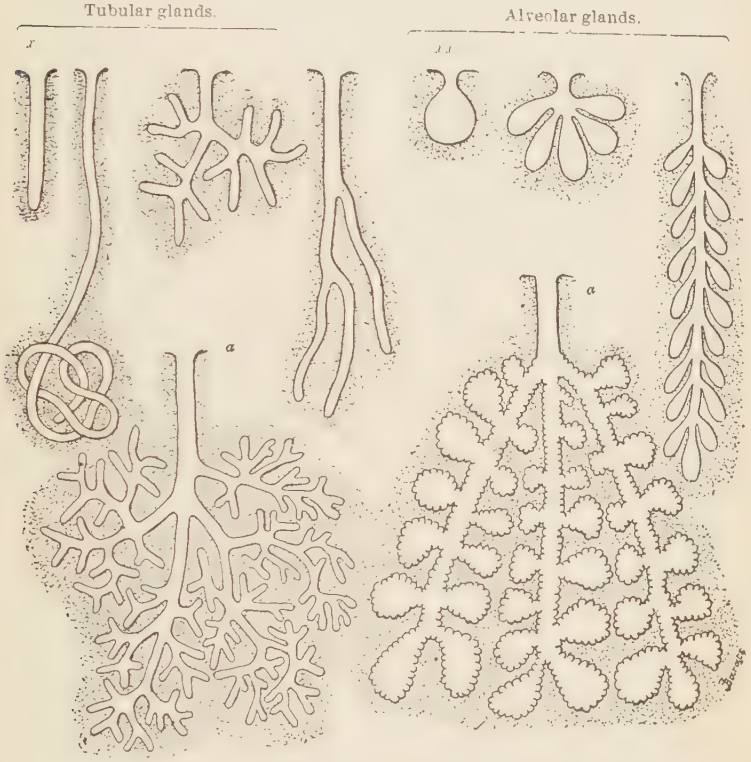

FIG. 18.—A diagram of various typical forms of glands. *a*, duct; *x*, simple tubule; *xx*, simple alveolus. (Szymonowicz and MacCallum.)

THE SECRETORY PROCESS.

The act of secretion consists primarily of the passage of a stream of water, containing various dissolved substances, from the tissue fluids (and indirectly from the blood), through the gland cells to the duct. The concentration of the secretion in dissolved substances is in most cases different from that of the tissue fluid from which it is derived, so that a part of the gland's function is to alter the

relative proportions of these substances. The majority of glands pour out a secretion that is more dilute than tissue fluid, showing that they act to hold back some constituents. The secretion of the kidney is usually more concentrated than tissue fluid, indicating an action in the reverse direction. During the passage of fluid through the gland cells whatever special substances the cells have to contribute are taken up and borne along.

Gland-cell Membranes and the Control of Secretion.—In most glands of the group under discussion there is some continuous secretion, indicating that the faces of the cells are sufficiently permeable to allow materials to pass to some extent, and that the metabolic processes associated with gland action are fairly continuous. A striking feature of these glands, however, is that with few exceptions their volume of secretion is greatly augmented by suitable stimulation. The adequate stimulus may be nervous, in which case it is exerted through the autonomic system (page 128); or it may be chemical, exerted through the action of hormones (page 140), which reach and influence the glands through the blood stream.

In either event the explanation which seems to account best for the facts of secretion assumes the stimulus to act by altering the permeability of the gland-cell membranes. The membranes mainly affected are thought to be those which form the *outer* faces of the cells. These faces must ordinarily be relatively impermeable, so that materials escape through them only slowly. They contrast in this respect with the *inner* faces of the cells, which are presumably freely permeable at all times to the water and inorganic solids of tissue fluid (subject to limitations imposed by the Donnan equilibrium, page 37), and to such organic raw materials as the cells require for their metabolism. These faces appear to be impermeable to the special secretory products elaborated by the cells; at least there is little indication that the characteristic products of glands of this type appear in the blood.

When adequately stimulated the outer (lumen) faces of the gland cells become permeable to all the materials that appear in the secretion, including water and dissolved substances that pass through the cells from the tissue fluids, as well as the characteristic products synthesized within the cells themselves. The result is an abundant out-pouring of the secretion.

The Mechanics of Gland Action.—The known physical forces that can play a part in connection with an outflow of fluid from gland cells are the hydrostatic pressure of the tissue fluid, derived directly from the pressure of the blood in the adjacent capillaries and indirectly from the force of the heart beat (page 342), and any osmotic pressure that may arise from differences in concentration of the fluids within and without the cells. The former force is constantly present, and undoubtedly is a factor of importance in

most if not all secretion by first-type glands. Its tendency is directly toward causing fluid to flow from tissue fluid to gland-duct. Osmotic pressure, on the other hand, acts in most glands strongly against rather than in favor of the formation of secretion. The fact has already been mentioned (page 136) that nearly all gland secretions are more dilute than the tissue fluid and blood plasma from which they are derived. The difference is particularly striking when expressed in terms of the hydrostatic pressure that just balances the difference in osmotic pressure between the secretion and the blood plasma. The osmotic pressure of plasma (which is in equilibrium with tissue fluid) amounts to about 6.6 atmospheres, or enough to sustain a column of mercury approximately 5000 mm. high. Saliva, by comparison, has an osmotic pressure of about 4 atmospheres, or 3000 mm. Hg.; the osmotic pressure of sweat varies under different conditions over a wide range; one fairly representative series of tests (Adolph) showed an average value of about 3.3 atmospheres (2500 mm. Hg.). It follows that if the out-pouring of fluid were solely a matter of sufficient hydrostatic pressure to overcome the difference in osmotic pressure between the secretion and the blood plasma a pressure of 2000 to 2500 mm. Hg. would be required. As a matter of fact the actual pressure in the gland capillaries probably never exceeds 100 mm. Hg., and is usually nearer one-half that figure (page 342). Some other force than that furnished by the heart beat must come into play, therefore, to overcome this great osmotic resistance. Incidentally it should be pointed out that some glands can force out their secretion against an actual fluid back pressure greater than the hydrostatic pressure of the blood in their vessels. This fact, which was extremely impressive when discovered, becomes less important in contrast with the much greater osmotic pressure that is also counteracted.

Diligent effort has been devoted to the search for some mechanical compression exerted within the gland, by which the osmotic resistance may be overcome. Thus far, beyond the demonstration that the gland shrinks during active secretion, no satisfactory progress has been made in this direction. No contractile structures capable of displaying the necessary force have been found.

Gland-cell Metabolism.—There is, however, a known source of as much energy as is required; although we have only theories as to how the energy may be applied. The source is in the functional metabolism of the gland cells (page 65). Glands are known to consume oxygen and give off carbon dioxide, and several times more abundantly during and shortly after secretion than when at rest. Representative figures are: for the submaxillary of a small dog, 0.25 ml. oxygen per minute while at rest; 0.86 ml. per minute while secreting actively (Barcroft). This increased oxygen consumption is clear evidence for the occurrence of exothermal reactions in

connection with secretion. The energy thus made available evidently serves to bring about the separation from the tissue fluid of a liquid having the composition in water and dissolved substances of the secretion, and to cause this fluid to pass through the gland cells to the duct with such assistance as the hydrostatic pressure of the tissue fluids themselves affords. From time to time investigators have been so impressed by the complexity of this process as to conclude that it depends on some "vital" force, outside the realm of ordinary physics and chemistry. The fact is, however, that the more insight we get into the process the more evident it becomes that definite physical and chemical principles govern it.

SEROUS AND MUCOUS CELLS.

Thus far we have considered only the problem presented by the passage of water and dissolved substances from tissue fluids through gland cells into ducts. Most glands of the group under discussion

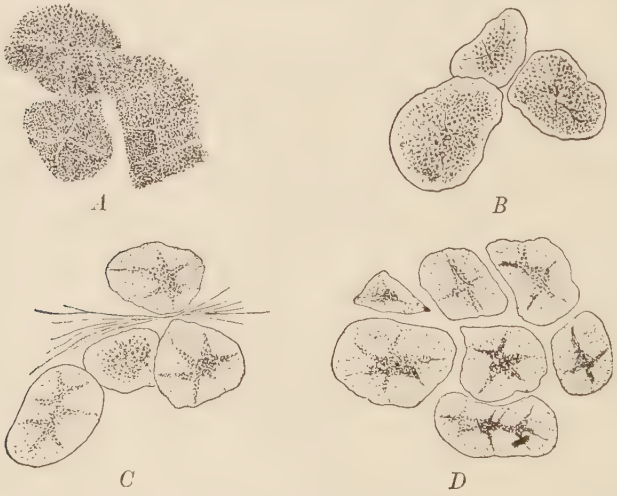

FIG. 19.—Part of an alveolus of the pancreas (rabbit). *A*, in the "resting" state; *B*, after active secretion; *C*, after more vigorous action occasioned by both pilocarpine and stimulation of the sympathetic; *D*, after long-continued action from stimulation of the sympathetic. (Langley.)

contribute to the secretion, as has already been stated, substances which are manufactured within them and added to the secretion as it passes through. A gland of this type shows, when in the "resting state," a great accumulation of minute structures, easily made visible by histological methods, within the cytoplasm. These structures diminish markedly, or may even disappear, during active secretion. There is good reason to believe that they are related

in some way with the characteristic products of the gland cells. Different glands produce different substances. The digestive glands, which make up the major part of the group we are now considering, give rise to the various enzymes which catalyze the essential chemical processes of digestion, and to a small number of other albuminous compounds, chief of which is the glycoprotein, *mucin*, a substance which seems to owe its chief significance to its marked viscosity. It appears that these two kinds of material are produced by different cells. The so-called *mucous* cells produce mucin and the *serous* cells enzymes. To a considerable extent the two types of cells are grouped separately, into mucous or serous glands respectively, or into mucous or serous alveoli in "mixed" glands. The separation is not absolute, however, many gland alveoli containing both types of cells. The parotid (page 390) is a good example of a serous gland; many minute mucous glands are present in the lining of the buccal cavity; the submaxillary (page 391) is a typical mixed gland.

ZYMOGEN AND MUCINOGEN GRANULES.

The enzymes found in digestive secretions are known not to be present in active form within the gland cells, but to be represented by inactive precursors, called *zymogens*. The minute structures spoken of in the last paragraph are called *zymogen* granules when present in serous cells and *mucinogen* granules when in mucous cells. The names imply that they are masses of inactive precursor material which contribute of their substance to the secretion as it is formed and so are used up. It is much more probable, as a matter of fact, that they are really specialized subportions of cytoplasm, differing chemically as well as functionally from surrounding portions, and hence set off by intracellular equilibrium membranes (page 40), within which the synthesis of zymogen or mucinogen proceeds. There is direct histological evidence that the out-pouring of enzymes or of mucin is attended by disappearance of granules. some observers have maintained that this process is under the control of a special set of nerves, entirely distinct from those that excite the out-pouring of the watery part of the secretion. The evidence for this view does not appear convincing at the present time, and physiologists are inclined rather to think of the break-up of the granules as a necessary result of the secretion of water and salts. The line of reasoning is as follows: The granules maintain their identity by virtue of the membranes which enclose them; these are equilibrium membranes, and hence subject to alteration when the composition of the medium on either side of them changes. With the initiation of the secretory process water and dissolved substances escape from the general mass of cytoplasm to the lumen of the gland.

This changes the external environment of the granules to an extent which leads to the partial break-down of their enclosing membranes, and so permits the zymogen or mucinogen to pass out into the surrounding cytoplasm, and thence into the secretion. The restoration of the initial state, in which the granules are fully charged with zymogen or mucinogen, depends, according to this view, on functional metabolism within the granule structures, of such a nature that raw materials entering the cytoplasm from the surrounding tissue fluids are synthesized into zymogen or mucinogen, according as the cell is serous or mucous.

The Conversion of Zymogen into Enzyme.—In an early chapter (page 54) evidence is cited indicating the fundamental components of enzymes to be large monovalent ions. Presumably the synthetic processes going on within zymogen granules produce these from available raw materials. The particular physico-chemical groupings characteristic of enzyme micellæ cannot be thought of as present in the granules, for if they were we should expect to be able to demonstrate active enzymes in resting gland cells, which has not been done. Apparently the grouping of constituents which makes enzymes functionally active occurs ordinarily either in connection with the discharge of zymogen from the granules into the cytoplasm at large or in connection with the passage of the secretion through the lumen faces of the cells into the ducts of the gland.

SECRETION UNDER HORMONE STIMULATION.

The description of gland function thus far has dealt only with effects obtained through nervous excitation. In addition to this means of evoking action some glands, notably the pancreas, can be stimulated chemically by hormones brought to them in the blood. The hormones are assumed to act by increasing the permeability of the lumen faces of the gland cells. A very important characteristic of the secretion poured out by the pancreas as the result of hormone stimulation is that one of its enzymes, the proteolytic enzyme *trypsin* (page 412), appears in the secretion in inactive form, requiring to be "activated" by a constituent of intestinal juice before it can display enzyme properties. Pancreatic secretion may be evoked in experimental animals by stimulation of the vagus nerves. In the juice thus obtained all the enzymes, including trypsin, are in active form. Why the gland should secrete inactive trypsin when stimulated chemically, and active trypsin when stimulated nervously, cannot be explained at present. The fact that under chemical stimulation the other two enzymes are secreted in active form shows that chemical excitation is not fundamentally different from nervous. The indication is rather that a specific influence exists, preventing the formation of active trypsin in the presence of the hormone.

Zymogen Exhaustion.—Most glands are capable of long-continued activity. In some, like the salivary glands, there occurs a depletion, or even virtual disappearance, of zymogen when the gland is active for a long time. This indicates that the synthesis of zymogen is a gradual process, which goes on chiefly during the intervals of rest between active secretion periods. The same view is favored also by the observation that the increased consumption of oxygen outlasts by a considerable interval the actual time of secretion. This prolonged oxygen-consumption implies exothermal reactions by which the cells are restored to their resting condition following activity. Depletion of zymogen granules does not imply loss of secretory power. Such glands as suffer exhaustion of their enzyme supply as the result of long-continued activity may continue thereafter to pour out a watery secretion. This fact lends further support to the view that the act of secretion proper is distinct from and independent of the synthesis of zymogen.

The pancreas shows the interesting feature of supplying even during long-continued activity a secretion in which the proportion of enzymes holds up to normal. This signifies that the synthesis of zymogens keeps pace with their discharge into the secretion. The difference between glands like the pancreas, in which enzyme exhaustion does not occur, and those like the salivary glands, which are subject to exhaustion, seems to be only in rate of zymogen synthesis, and does not so far as can be judged indicate a fundamental distinction in gland character.

SECRETION OF HYDROCHLORIC ACID.

Gastric juice, the secretion of the gastric glands, contains a moderate concentration of hydrochloric acid (about 0.03 per cent in man). The mechanism by which this simple inorganic acid is formed and separated from the cytoplasm of the gland cells is difficult to picture. One theory suggests that ammonium chloride is formed in the parietal cells of the gastric glands through the interaction of sodium chloride, abundantly present in cells and tissue fluids, with an ammonia compound, perhaps ammonium carbonate, known to be an occasional product of cellular metabolism. The ammonium chloride is assumed to escape into the gland lumen and there to suffer hydrolytic dissociation into hydrochloric acid and basic ammonia. The further assumption is made that the lumen faces of the gland cells are permeable to the base but not to the acid, leading to reabsorption of the ammonia by the cells, leaving the acid free in the lumen. Another theory pictures proteins as entering into union with hydrogen and chlorine, the product undergoing subsequent decomposition in such fashion as to leave the acid free in the gland lumen. There is evidence that the hydrogen-ion con-

centration within the lumen is higher during secretion than it ever rises within the living gland cells; also that the lumen faces of the cells are impermeable to acid during health. This latter fact helps to explain why the healthy stomach wall is not injured by its own acid secretions, which are strong enough to attack some sorts of living cells.

Three kinds of glands, the tear glands, the sweat glands, and the kidneys, belong in the group under discussion in that they pour their secretions into surfaces communicating with the outside of the body. They differ from the digestive glands in not synthesizing and pouring out enzymes, hence form a separate subgroup to be considered next in order.

TEAR GLANDS.

These correspond to the general picture of gland function already given (page 135) in that they separate out from the blood a fluid poorer in salts than blood plasma, and so involve a display of energy on the part of the gland cells. They correspond also in that the actual outpouring of the secretion is aroused by nervous excitation. The chief inorganic constituent of tears is sodium chloride, present in concentration of about 0.14 per cent (0.025 mol.). The other inorganic constituents of blood plasma occur in tears only in traces. A mucin-like compound is contributed by the gland cells, although in much smaller proportion than in typical mucous glands.

SWEAT GLANDS.

The sweat glands, like the tear glands, are under nervous control. They separate out from the blood a dilute fluid consisting wholly of water and non-colloidal plasma constituents. No contributions are made by the gland cells themselves. Sweat sometimes contains bile pigments, showing that under excitation the lumen faces of the cells may become permeable to molecules of considerable size. Sodium chloride is the chief inorganic, and urea the chief organic constituent of sweat. Ammonia compounds are also constantly present, imparting a characteristic odor. Urea and ammonia are normally more concentrated in sweat than in blood; all other dissolved constituents are less concentrated (Plaggemeyer and Marshall). The hydrogen-ion concentration is on the acid side of neutrality, although in prolonged sweating the reaction becomes less acid.

The formation of a dilute secretion implies the occurrence of energy-yielding reactions within the gland cells. That exothermal reactions attend the production of sweat is shown by a demonstrable augmentation of carbon dioxide production in the skin whenever

sweating is profuse. The function of sweat is to aid in heat-elimination by evaporating from the skin, and so carrying off from the body the heat of vaporization. The details of its action are discussed under the head of Temperature Regulation (page 449).

THE KIDNEY TUBULE.

The secreting unit of the kidney is the tubule, a structure consisting essentially of a terminal *capsule* containing a tangled mass of capillaries making up the *glomerulus*, and a tubular passage leading

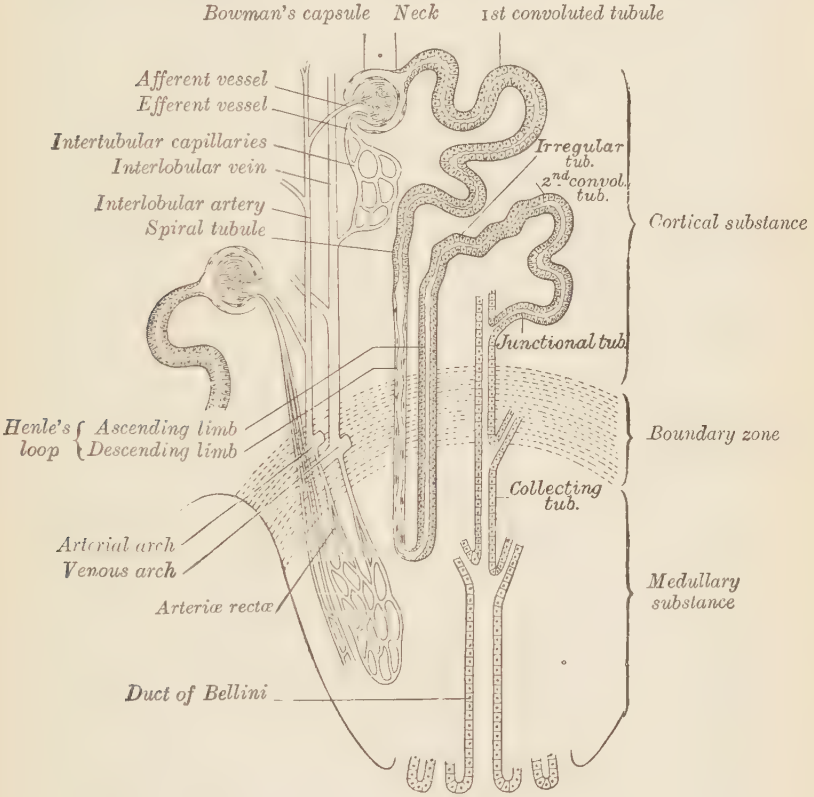

FIG. 20.—Scheme of renal tubule and its vascular supply. (Gray's Anatomy.)

from the capsule to points of union with similar passages from other capsules, and thence to the hilus of the organ. The significant structural features are: (*a*) The arrangement of the capillaries of the glomerulus in such a manner as to secure a higher capillary pressure than obtains elsewhere in the body (for further discussion of this point see page 355); (*b*) an exceptional thinness of the mem-

brane of the capsule, which membrane, in addition to the walls of the capillaries themselves, is all that stands between the blood in the glomerulus and the lumen of the tubule; (*c*) the composition of portions of the tubule walls of cells similar in appearance to ordinary secreting gland cells, and, like gland cells in general, provided with a rich blood supply.

Capsules Appear to Act as Mechanical Filters.—There is direct evidence that during the flow of blood through the glomeruli a clear liquid separates out and enters the lumen of the capsules, passing thence to the lumen of the tubules. The liquid has been shown to contain all the easily identified blood constituents except the proteins, phosphatides, and allied compounds. The evidence has been obtained by thrusting micro-pipettes directly into the lumen of individual capsules (in frogs and salamanders), collecting the escaping fluid, and submitting it to microchemical analysis (Wearn and Richards, also White and Schmitt). Long before this direct evidence was obtained; indeed from the first recognition by Bowman (1842) of the relation of the Malpighian body to the tubule, the capsule had come to be looked upon as essentially a filter in which the fluid appearing in the capsule lumen is separated from the blood by simple mechanical filtration, and therefore consists of blood plasma, minus any constituents whose molecules are too large to pass the filtering membrane, which in this case is composed of the combined capsular and capillary walls.

Assuming the action to be mechanical filtration the filtering force must be the hydrostatic pressure of the blood in the glomerular vessels as maintained by the force of the heart beat, since no other force can be conceived as in position to be brought to bear. For filtration to occur this pressure must be greater than the sum total of opposing forces. Among the latter are the resistance of the membrane itself, the back pressure of the filtrate (under normal conditions not significant), and the osmotic pressure of the substances that remain behind in the blood because their molecules are too large to pass the filter. This last factor is of particular importance. For one thing it implies as of necessity that the membrane shall be freely permeable to nearly all dissolved constituents of blood. The hydrostatic pressure in the glomerular vessels rarely if ever mounts to 100 mm. Hg. (see page 355). It is probably normally considerably below that figure. But only small amounts of dissolved substance are required to bring the osmotic pressure of a solution above 100 mm. Hg. The inorganic salts of blood plasma have, as already stated (page 137), an osmotic pressure of about 6.6 atmospheres, or 5000 mm. Hg.; the dextrose in solution in blood is present only in about 0.1 per cent concentration, yet its osmotic pressure is equivalent to 95 mm. Hg.; the urea is still more dilute, having

only 0.028 per cent concentration, but it exerts an osmotic pressure of 77 mm. Hg. Blood plasma that has been freed of all these constituents has still an effective osmotic pressure of between 20 and 30 mm. Hg. (Starling and others). Before direct tests of the glomerular filtrate had shown it to contain inorganic salts, urea, and sugar the presence of these substances in it had been postulated, and the effective osmotic pressure to be overcome assumed to be that of plasma minus these constituents, *i. e.*, about 30 mm. Hg. In support of this assumption is the observation that when the hydrostatic pressure of the blood in the kidney vessels falls to about the above level urine formation ceases.

Reabsorption and Secretion in the Convoluted Tubules.—The urine that passes down the ureters from the kidneys to the bladder differs markedly from the fluid which filters through the capsular membranes. Some substances present in the filtrate are wanting from urine, except for slight traces (sugar is the most important example); others are present in quite different concentrations. Changes in composition evidently occur during the passage of the fluid along the convoluted tubules. A great number of investigations have been devoted to the attempt to determine the precise nature of these changes. None of them have yielded wholly convincing evidence, although their combined effect has been to establish a theory accepted, with minor variations, by nearly all workers. To illustrate the nature of these investigations some observations of Starling and Verney will be described. These workers studied urine formation in excised mammalian kidneys perfused with blood. Such preparations, under proper experimental conditions, continue to secrete a fluid not too widely different from normal urine for a fairly long period. When cyanide is added to the blood passing through one of these kidneys the convoluted tubules are assumed to cease functioning so long as the cyanide effect endures, but the glomeruli to be unaffected. The argument on which this assumption rests is that the tubules act like ordinary glands, hence cease functioning when oxidation processes are suppressed within them (suppression of oxidation is recognized as the typical effect of cyanide on protoplasm, page 51). The glomeruli, on the other hand, being simple filters, do not depend on oxidation for their ability to function, and so may be presumed to be unaffected by the cyanide. In support of the assumption is the finding that kidneys poisoned with cyanide produce a "urine" virtually identical with blood plasma minus its colloids. The obvious explanation is that when oxidation processes are suppressed the glomerular filtrate forms as usual, but passes through the convoluted tubules without being acted on by their cells, and hence emerges at the hilus of the kidney unchanged in composition. The objection that may be, and has

been, urged against this experiment is that cyanide may injure the glomeruli as well as the tubules. Granting that the normal glomeruli act as filters the fact that "urine" formed by a cyanided kidney is virtually identical with non-colloid plasma proves that the cyanide has not brought about any *qualitative* change in glomerular action; whatever effect it has must be on the *quantity* of filtrate formed.

Normal urine is about four times as concentrated as blood plasma in respect to total non-colloid solids. Some or all of this difference in concentration is to be accounted for by supposing the volume of glomerular filtrate to be greater than of finished urine, and a *reabsorption* of part of the water to occur, reducing the final volume to the observed amount, and concentrating the constituents of the filtrate to correspond. In the experiments of Starling and Verney the volume of "urine" formed per unit of time by a cyanided kidney was always larger than of an uncyanided preparation. On the average the difference was somewhere near two to one, showing that about as much water was reabsorbed by the tubule cells in these excised and perfused kidneys as passed along to appear in the urine. The experimental procedure appears to have cut down the effectiveness of the uncyanided kidney preparations considerably, since other evidence indicates strongly that the proportion of water reabsorbed in the intact human kidney is ordinarily much larger than this. There is a disease, *diabetes insipidus*, characterized by formation of abundant and very dilute urine, in which the only demonstrable kidney defect is lessening of reabsorptive power for water (page 438). In this disease the total volume of urine is frequently 10 times normal, while in a few extreme cases volumes 16 or 17 times normal have been observed. The obvious conclusion is that glomerular filtration is normally at least 10 times the volume of finished urine, and reabsorption of water correspondingly active. A prominent theory of kidney function (that of Cushny), holds filtration to be much greater than this; in fact to be 60 or more times the volume of finished urine. The present trend of evidence appears, however, to indicate a figure nearer that suggested by diabetes insipidus, *i. e.*, 2 to 20 times the volume of finished urine.

The effect of reabsorption of part of the water is obviously to raise the concentration of the dissolved substances in the filtrate. If reabsorption of water were the only action of the tubule cells all dissolved constituents of the filtrate would necessarily be concentrated to exactly the same extent. As a matter of fact, however, they are concentrated very differently, as shown in the accompanying table from Cushny (slightly modified).

	Blood plasma, per cent.	Urine, per cent.	Change in concentration in kidney.
Water	90–93	95.000	
Proteins, fats, etc.	7– 9		
Dextrose	0.1000	Trace	
Urea	0.0300	2.000	60.0
Uric acid	0.0020	0.050	25.0
Na	0.3200	0.350	1.0
K	0.0200	0.150	7.0
NH_4	0.0010	0.040	40.0
Ca	0.0080	0.015	2.0
Mg	0.0025	0.006	2.4
Cl	0.3700	0.600	1.6
PO_4	0.0090	0.270	30.0
SO_4	0.0030	0.180	60.0

The differences in degree of concentration change are so wide as to point clearly to an active influence exerted on each individual constituent, quite apart from effects due to reabsorption of water. This influence may be either reabsorption or active secretion. Conceivably some one substance in the above list might be neither absorbed nor secreted by the tubule cells, in which case it would serve as a useful index to the extent of reabsorption of water, but the present weight of evidence is against the probability. The conclusion justified by current knowledge is that the substances present in urine in relatively small concentration, dextrose (also amino-acids) and the chlorides of sodium, calcium and magnesium, are reabsorbed in large or small degree, making their concentration in urine always *less* than it would be if the only change were due to reabsorption of water. Urea, uric acid, the phosphates and sulphates of potassium and ammonium, and some other constituents, such as creatinine, not mentioned in Cushny's table, appear to be actively secreted by the tubule cells, so that the quantity of each ultimately appearing in urine is the sum of what filters from the capsules plus what is secreted. The concentration of substances of this class is always *greater* than it would be if the only change were due to water reabsorption.

Kidney Action Involves Expenditure of Energy. Both reabsorption and secretion involve the overcoming of either hydrostatic or osmotic resistances, and hence imply the expenditure of energy. The seat of energy expenditure is obviously in the cells of the convoluted tubules, and the source of the energy is evidently the same as in ordinary secreting glands, namely, oxidation of fuel. There is positive evidence that the kidney carries on oxidative processes in connection with urine formation. The mechanism by which the energy is utilized may or may not be similar to that by which a corresponding result is obtained in other glands. Future work should settle the question.

Synthesis in Kidney Cells. – The kidney is predominantly an organ of excretion, and has no function so far as known of synthesizing

valuable secretory substances. It is interesting, however, that in the course of its activity as an excretory organ it does perform a certain amount of synthesis which serves a useful purpose. One function of the kidney is to eliminate "fixed" acids (page 166). In connection with this process there is formation of ammonia which combines with the acids and thus conserves other bases, while enabling the acids to be passed out as neutral salts. The ammonia produced for this purpose has been shown to be produced in the kidney itself (Nash and Benedict); the source is in the amino-acids present, whose NH_2 groups may be split off as in ordinary deamination (page 182).

Many fruits and vegetables, cranberries in particular, contain compounds which yield benzoic acid on oxidation. This acid is made non-toxic by union with glycine (amino-acetic acid), the first of the amino-acid series. The product is hippuric acid, found regularly in the urine of horses and other herbivora; in human urine only after the ingestion of benzoic acid precursors. The reaction between benzoic acid and glycine undoubtedly takes place in the kidney cells; recent work (Kingsbury and co-workers) indicates that it may also go on in other cells. Many body cells are known to synthesize glycine from other amino-acids (page 62), hence while synthesis of hippuric acid may be largely a special property of the kidney, in neither ammonia formation nor glycine synthesis is the organ unique. The products of these syntheses are secreted directly from the tubule cells into the urine.

Elimination of Alcohol and Allied Compounds.—Certain substances, of which alcohol is the most familiar example, occur in urine in nearly the same concentration as in blood plasma. The inference is that the walls of the convoluted tubules are very freely permeable to these compounds, while the tubule cells are "indifferent" to them, neither absorbing nor secreting them actively. They would then come by simple diffusion into equilibrium in blood and urine, the observed approximate equality of concentration in the two fluids necessarily resulting. Further discussion of kidney action will be found, beginning on pages 355 and 432.

SEBACEOUS SECRETION.

A group of glands represented by the sebaceous glands of the skin contribute secretions to body surfaces. These appear simpler in action than the other types inasmuch as the out-pouring of material is accomplished by gross rupture of the lumen faces of the cells and the sloughing of the whole outer portion of the cells into the lumen of the gland. Prior to this process there is synthesis of the characteristic material secreted by the gland; in all glands of this type the secretion is fatty or waxy in nature. It is concentrated in

the outer part of the cell to such an extent that little else remains there. When the lumen face ruptures and the accumulated material passes out the cell membrane reforms over the cytoplasm remaining, opening the way for a repetition of the whole process. The mammary glands are looked on as modified sebaceous glands (page 760).

ENDOCRINE GLANDS.

The second great group of glands includes those that pour their secretions into the blood instead of onto surfaces. These are the glands of internal secretion, known also as *endocrine* glands (endocrine—separated within). The substances produced by glands of this type are chiefly *hormones* (page 55, also Chapter XII). So far as the synthesis of specific substances out of raw materials obtained from the blood is concerned the same principles are supposed to apply as in first type glands (page 139). In many endocrine glands either nervous or chemical excitation is necessary to induce an out-pouring of secretion. We may suppose that in these, as in digestive or other glands that act similarly, increase in cell-membrane permeability results from the nervous or chemical excitation, the discharge of material following directly.

The hydrostatic situation presented in the endocrine glands is quite different from that seen in other glands. There is no reason to assume any special movement of water; the cells front on tissue fluids on all exposed surfaces; there is virtual osmotic equilibrium between the cell contents and the medium into which the secretion is to be discharged. The secretory process may accordingly be thought of as essentially a simple dialysis of the specific hormone from a region of high concentration to one of lower. The dialysis would be held in abeyance so long as the cell membrane were unexcited; stimulation, by making the membrane permeable, would initiate the secretory process.

Individual hormones are dealt with in later chapters, where their particular roles in bodily functioning are under consideration.

Summary.

Glands are grouped as of *external secretion*, when they pour their products into surfaces that communicate with the exterior, and of *internal secretion* (endocrine glands) when their products pass into the blood.

In glands of the first group, typified by the digestive glands, a stream of water and dissolved substances passes from the tissue fluids through the gland cells to the duct, picking up in its progress the characteristic substances contributed by the gland; these are, in digestive glands, mainly mucin, contributed by mucous cells, and one or more enzymes, contributed by serous cells.

In such glands as are under either nervous or chemical control the effect of excitation is supposed to be an increase in permeability of the lumen faces of the gland cells, making these faces freely permeable to water and dissolved substances, and also to the specific products of the cells. The inner faces of the cells are looked upon as permeable at all times to water and dissolved substances and to the raw materials which must enter the cells from the blood to provide for their metabolism, but not to the specific substances which the cells produce.

Moderate hydrostatic pressure exerted by the blood favors the act of secretion. This is counteracted many times over, however, by a reverse osmotic pressure in most glands, since typical secretions are considerably more dilute than the tissue fluids. The mechanical means by which this osmotic pressure is overcome is not understood, although the required amount of energy is known to be furnished by oxidation processes included in the functional metabolism of gland cells.

The specific substances which glands of the digestive type contribute to their secretions are present within the gland cells in inactive precursor forms, known as zymogens or mucinogens. These are apparently synthesized within subportions of the cytoplasm set off from the general mass by intracellular membranes; the subportions are called *zymogen granules;* in the case of mucous cells, *mucinogen granules.*

The discharge of zymogen or mucinogen from granules into the cytoplasm at large, and thence into the secretion, is thought to result directly from changes in the granule membranes, which changes follow, in turn, the alteration in the previously existing equilibrium brought about by the passage of water and dissolved substances out of the cells into the duct. This view does not admit the existence of special nerves whose function is to excite the granules to discharge their contents.

The conversion of inactive precursors into active constituents of the secretion is thought to take place either in connection with the discharge of the granules or with the passage of the secretion through the lumen faces of the gland cells.

The restoration of the initial state, including fully charged granules, appears to depend on metabolic activity in which there is marked consumption of oxygen; in many glands this process lags behind the active processes of secretion; such glands are apt to become exhausted in respect to their power of contributing specific substances, although not affected in their ability to pour out water and dissolved materials furnished by the tissue fluids.

Some glands, notably the pancreas, are excited to active secretion by specific hormones brought to them through the blood. It is assumed that the effect of these is to increase the permeability of the

lumen faces of the gland cells; the action is thus equivalent to nervous excitation. The pancreas, under chemical excitation, discharges trypsin, one of its three enzymes, into the secretion in the form of inactive trypsin. Since the other two enzymes are discharged in active form this cannot be looked on as a necessary consequence of chemical excitation; it is more likely a specific relationship between the particular hormone and trypsin. In support of this view is the fact that when the pancreas is stimulated nervously it discharges all three enzymes in active form.

Gastric juice contains free hydrochloric acid. One suggestion to explain the separation of this from the tissue fluids is that ammonium chloride, formed by a reaction between sodium chloride and ammonium carbonate, passes the lumen faces of the parietal cells of the gastric glands and enters the duct of the gland. Here a dissociation into hydrochloric acid and basic ammonia is postulated; the latter substance is assumed to be taken up by the gland cells, leaving the acid in the duct. Another view looks on proteins as the agencies by which acid is separated and set free.

Tear glands and *sweat glands* are susceptible to nervous excitation. Both types separate out a secretion of lower osmotic pressure than the tissue fluids, implying an expenditure of energy on the part of the gland cells. Except for a small amount of mucin in tears neither of these types of glands contribute specific materials synthesized within their cells.

The unit of kidney action is the tubule. The physiologically significant parts are the *capsule*, enclosing a mass of capillaries known as the *glomerulus;* and the *convoluted tubule*, composed of cells structurally similar to secreting gland cells.

There is positive evidence that the *capsules act as filters*, separating out from the blood plasma a liquid identical with it, except for proteins and phosphatides, which do not normally pass the filter. Present information indicates the volume of filtrate to be two to ten times as great as of finished urine, implying a reabsorption of part of the water. This reabsorption occurs in the convoluted tubules.

Present information indicates, furthermore, that in addition to reabsorption of water there is *reabsorption by the tubule cells* of dextrose and of sodium, calcium, and magnesium chlorides (presumably also of amino-acids, although this has not been sufficiently investigated). The *tubule cells secrete* urea, uric acid, and the phosphates and sulphates of potassium and ammonia; also certain other regular or occasional urinary constituents with large molecules.

Both reabsorption and secretion imply an expenditure of energy on the part of the tubule cells. The energy is made available by oxidation processes. The mechanism by which it is applied is unknown.

The tubule cells have the property of synthesizing hippuric acid when benzoic acid precursors are taken up from the alimentary tract by the blood. They may also synthesize glycine from other amino-acids, and ammonia by separating off NH_2 groups from amino-acids. Neither of the last two actions is specific for kidney cells. The first appears to be largely but perhaps not entirely so.

Alcohol and certain other substances appear in urine in nearly the same concentration as in blood. The explanation offered is that the tubule cells are "indifferent" to these substances, and also so freely permeable to them that diffusion equilibrium between blood and urine is quickly attained.

Glands of the sebaceous type secrete an oily or waxy material which is synthesized within the gland cells and poured out by sloughing of the whole outer portion of the cells.

Glands of internal secretion, known also as *endocrine* glands, produce *hormones*. The synthesis of hormones from the raw materials furnished by the blood is presumably along the same general lines as the production of enzymes by the cells of the digestive glands.

Some endocrine glands are known to pour out their secretions under nervous or chemical excitation. Presumably an increase in cell-membrane permeability is the essential factor. The process of secretion appears to be simple dialysis from the cell cytoplasm through the cell membranes into the surrounding tissue fluid.

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(For other works on kidney function, see end of Chapter XXVII.)

PART II.

CELL ENVIRONMENT.

CHAPTER X.

CELL ENVIRONMENT: TEMPERATURE; WATER CONTENT; HYDROGEN-ION CONCENTRATION.

Cells in Relation to Environment.—In chapters preceding this one living cells have been considered as systems capable of certain definite activities. The nature of the activity in every case is determined by the organization of the protoplasm of which the cells are composed. The basis of activity is in all cases chemical or physico-chemical, the reactions being grouped under the generic term metabolism. The design has been to show clearly that the orderly performance of the life processes results automatically from the organization of the protoplasmic system. This system has been pictured, moreover, as an equilibrium system, in which the interrelations between the various parts of individual cells, and between the cells as units and the fluid medium surrounding them, depend on the chemical, physico-chemical, and physical conditions prevailing within the cells, on the one hand, and in the external medium on the other. It follows that cells are affected by every change in the environment; more by some than by others; favorably by some and unfavorably by others. An environment that is reasonably favorable to cell life and cell function may be called normal; one that is so unfavorable as to threaten life or to disturb function is abnormal.

Healthy Life Depends on Normal Cell Environment.—In Chapter IV (page 65) is mention of the view that metabolism has by-products which fail of elimination and so gradually accumulate within the protoplasm to the impairment of the metabolic processes. Senility, according to this view, is due to the accumulation of these metabolites. Assuming this to be correct we have in man one condition from which there is no escape, which will sooner or later bring life to an end. Medical science is not in position as yet to concern itself seriously with this possibility. For practical

purposes we may neglect it, and so be in position to accept the following general proposition: *If ideal cell environment could be maintained continuously about every cell in the body all of them would continue to function correctly, and normal healthy life would go on indefinitely.* Admitting the above to be true it follows that the task of Physiology, after it has dealt with the basic facts of protoplasmic functioning, becomes that of determining the factors which constitute suitable cell environment; the limits of variation of each within which normal metabolism can go on; how metabolism itself affects the environment; and finally how, in the complex body of man, the various cells and groups of cells act to maintain or modify the environment of one another. To this task the remaining chapters are chiefly devoted. Incidentally the task of Medicine may be stated as that of determining when departures from suitable cell environment have occurred; what has caused them; their nature; their effect; what can be done toward restoring suitable environment; and how to do it.

Factors in Cell Environment.—The factors making up cell environment fall under the following main heads (the order is that in which they are discussed in subsequent chapters): (*a*) Temperature; (*b*) water content; (*c*) hydrogen-ion concentration; (*d*) inorganic salts; (*e*) nutrients, *i. e.*, energy-yielding foods; (*f*) vitamins; (*g*) miscellaneous dietary constituents, including drugs; (*h*) hormones; (*i*) bacterial toxins and the immune substances produced by the cells in reaction to them; (*k*) oxygen; (*l*) miscellaneous metabolites; (*m*) various external energy effects. Heading *g* is not given extended treatment here, inasmuch as it forms the subject matter of much of the allied field of pharmacology; incidental references to effects of drugs and other miscellaneous dietary constituents are found in subsequent chapters. Heading *i* is too extensive to be dealt with adequately in a work on physiology. Books on bacteriology and immunology should be consulted for details; a brief outline of the main facts of physiological interest is given in Chapter XVI. Heading *m* deals with a group of factors calling for a different method of presentation than is used with the others. These factors are considered separately in the latter part of the book (see also page 196 for facts concerning short-wave radiation).

TEMPERATURE.

Temperature as a factor in cell environment is important in two respects. In the first place there are upper and lower limits beyond which life is impossible; in the second place the rate at which metabolism proceeds varies with the temperature.

When all known kinds of protoplasm are considered the ultimate temperature range compatible with life is found to be quite wide.

In the dried state some spores survive temperatures as low as of liquid air, only a few degrees above absolute zero. When this was discovered it was offered as a suggestion (Arrhenius) to account for the beginning of life on the earth, by assuming life to have been brought by spores which traversed space from some other heavenly body, surviving the extremely low temperatures to which they would necessarily be exposed in making such a journey. The suggestion is interesting, but of no particular biological value as an aid to understanding the origin of life. It merely transfers the problem from this to some other planet. Dried spores are also known that will endure temperatures 15° or 20° C. above the boiling-point of water for an hour or more without injury.

Temperature Limits for Active Protoplasm.—The temperature limit for protoplasm in its usual watery state is, on the low side, −0.5° to −3° C. The exact limit depends on the concentration of dissolved inorganic salts, since this is the determining factor in establishing the freezing-point in systems like protoplasm. There is an abundant antarctic fauna, largely of echinoderms, inhabiting sea water of which the temperature never rises above 0° C.

On the high side the limit is set by the temperature at which proteins coagulate. For most animal proteins this is between 43° and 46° C. "Cold-blooded" animals, which include all kinds except mammals and birds, endure without harm any and all temperatures between the low and high limits just given. Mammals and birds are "warm-blooded," which means that their bodies maintain a nearly uniform temperature somewhere between about 35° and 40° C., at all times except during hibernation (see below). In this they differ from "cold-blooded" animals, which take the temperature of the surroundings within a degree or two. The upper limit of temperature for *individual tissues* of warm-blooded animals is near 44° C., agreeing in this respect with cold-blooded forms. The low limit varies widely among different tissues. Some that are quite tenacious of life, like mammalian nerve trunks and large bloodvessels, can be cooled practically to the freezing-point of water without being killed. When the feet are very cold their superficial temperature may go below 20° C. without injury (Benedict). Certain of the delicate structures of the central nervous system in man are apparently injured beyond recovery, on the other hand, by temperatures around 25° or 26° C. Since survival of the body as a whole hinges on continued functioning of these central nervous structures a drop of body temperature to the above level is fatal. In hibernation, which is a curious change of bodily condition taking place in winter in some species of mammals, body temperature may fall well toward the freezing-point without damage to any important tissues.

Human Body Temperature.—The normal temperature of the human body is given as 37° C. (98.5° F.). This is the temperature underneath the skin, and is an average for the entire twenty-four-hour day. The actual temperature in health ranges in the course of the day about 0.5° C. above and below the average; a transient rise of as much as 2° may occur as the result of very vigorous exercise or exposure to intense heat. It is noteworthy that complete bodily well-being is closely linked with the maintenance of this narrow range of normal temperature. The continuance for more than a few minutes of body temperatures as much as 2° either above or below the normal average is attended with symptoms indicating that cell environment has become unfavorable in respect to this factor.

Optimum Temperature.—The effect of rise in temperature is to quicken all bodily processes. This follows of necessity from their character as physical, physico-chemical, or chemical. There is an upper limit to the quickening, set by the tendency of heat to become destructive to living protoplasm as the coagulation temperature of protein is approached. The influence of this destructive tendency, operating against the quickening due to warming, results in the existence of a most favorable, or *optimum*, temperature, which for most bodily processes is a few degrees below the upper limit at which life can go on. One of the interesting facts of physiology is that the bodies of warm-blooded animals are kept near the optimum temperature through the functioning of an automatic heat-regulating mechanism (page 446). A departure from normal temperature, such as occurs in fever, means that this mechanism has been disturbed in some way.

The Temperature Coefficient.—Since warm-blooded animals preserve substantially uniform temperatures their tissues are largely exempt from effects due to warming or cooling. In cold-blooded animals and in excised tissues of mammals or birds during their period of survival, on the other hand, changes in temperature necessarily have profound effects, through their influence in changing the velocity of metabolic processes. It is a familiar fact that all cold-blooded animals are relatively sluggish when cold and relatively active when warm. Studies of excised tissues both of cold- and warm-blooded animals show that all metabolic processes and the activities that result from them are hastened by raising the temperature. One can plot the increase in activity in an experimental tissue against the rise in temperature, according to the well-known methods of plotting curves, and obtain a mathematical expression for the effect of temperature changes on the activity of the tissue studied. The term "temperature coefficient" is used to indicate the proportional quickening that results from an increase in temperature of 10° C. For complete accuracy

the initial temperature should also be stated. In general, purely physical processes have temperature coefficients below 2; in other words raising the temperature 10° C. does not double the velocity of the process. Purely chemical processes, on the other hand, have coefficients above 2, showing that a rise of 10° C. more than doubles the velocity. Physiological activities are usually partly physical and partly chemical, and in correspondence they usually show coefficients intermediate in value.

Heat Transfer a Factor in Temperature Regulation.—All tissues produce heat in connection with their basic metabolism, and all that function actively produce more in connection with their functional metabolism. This heat is transferred to the immediate cell environment, tending to raise the temperature of the latter. There must be a further transfer, either to other cooler regions of the same body or to the exterior; failing this the temperature about the heat-producing cells would rise continuously, to their ultimate destruction. The automatic control of this heat transfer constitutes the temperature-regulating mechanism referred to above.

WATER CONTENT.

Water content is obviously of great importance both to cells and to their environment. The simple facts that nearly 75 per cent of the mass of most animal protoplasm is water, and that water acts as the vehicle by which all supplies are brought to the cells, and both waste products and excess heat removed, are sufficient to emphasize this. Water is readily available from the exterior for most animal forms; it also is produced and set free continuously within all cells in the course of their metabolism. A molecule of water is formed for every two atoms of hydrogen oxidized; furthermore, the large molecules of sugar, fats, and other substances that enter into metabolism have water molecules adhering to them that are set free in the course of metabolism. It is stated that each gram of glycogen in the body is thus loosely combined with about 4 gm. of water (Marriott). Water derived from either of these sources, the so-called "water of metabolism," makes up in all animals an important part of the total water supply. In desert forms, including such mammals as prairie dogs and desert sheep, which may never drink water, and in such insects as clothes moths, water of metabolism comes very near satisfying the entire need of the organisms; the only supplementary source being the water included in the more or less dry food.

Assuming an animal to have sufficient water in its body to start with, it is clear that the need for taking in additional water is due to the loss of some from the body. If the loss could be cut down so as not to exceed the water of metabolism an animal could

get along indefinitely on air-dry food. The factors regulating water-loss evidently determine how extensively drinking of water must be resorted to.

Distribution of Water in the Body. –About 60 per cent of the mass of the average body consists of water, or about 42 kilos in a 70 kg. man. This water is present in three states: (*a*) Inside the cells as protoplasmic water; (*b*) incorporated within the hard structure of bone and cartilage; (*c*) occupying the bloodvessels, the intercellular spaces (including lymph channels), and the subcutaneous and serous spaces, as free water. The proportional distribution can be only roughly estimated. The subjoined table will serve to give an idea of it.

ESTIMATED DISTRIBUTION OF WATER IN THE BODY OF A 70 KG. MAN.

	Kilos.
Protoplasmic water (75 per cent of 40 kilos, estimated mass of active protoplasm)	30.0
In hard structure of bone and cartilage (22 per cent of 11 kilos)	2.5
Blood plasma (p. 250)	2.0
Intercellular liquid (10 per cent of 55 kilos, estimated total mass of soft tissues)	5.5
In subcutaneous and serous spaces	2.0
Total	42.0

The chief significance of the above table in the present connection is not in the accuracy of its data, for which no particular claim is made, but to call attention to the fact that the amount of water available to serve as immediate cell environment (intercellular liquid) is relatively small, and that which functions as a vehicle for the transport of material (blood plasma) still smaller.

The Status of Protoplasmic Water.—There is every reason to suppose that water enters into the structure of protoplasm as definitely as any other of the compounds present. Some of it is presumably bound by molecular attraction both with the micellæ (page 22) and with all dissolved molecules, large and small, that undergo hydration in water. The remainder is free, functioning as a solvent for soluble constituents of the protoplasm, and as the continuous phase of the protoplasmic colloids. A point of great significance is that there is an optimum water content for any given sort of protoplasm toward which it always tends when conditions permit; this optimum depends in part on the amount of material present to hold "bound" water, and in part on factors, mainly osmotic, that operate to prevent protoplasm from becoming either excessively dilute or unduly concentrated.

The Effect of Metabolism on Protoplasmic Water.—Since the metabolic processes involve decomposition of many large hydrated molecules there is constant release of "bound" water in the course

of metabolism. There is also continuous production of water from oxidation of hydrogen. The water thus set free tends to raise the volume of "free" water above its optimum, and so leads to expulsion of water from the cells. Unless the cells are being starved this action is counterbalanced in the long run by the uptake of water along with the nutritive substances that make good the losses due to metabolism. We have to think of the cells, therefore, as losing water whenever metabolism outruns the uptake of materials, and as gaining water whenever the balance is in the reverse direction.

The Relation of Protoplasmic Water to Intercellular Water and Blood Plasma. The intercellular spaces are relatively small and in most parts of the body little subject to distention except by displacement of tissues as in edema. Since they are full of fluid all the time it follows that they have an extremely small capacity for additional water. As fast as water of metabolism enters them, therefore, they tend to pass it on to the blood. The volume of blood tends strongly, however, to be constant (page 271), hence the excess is again passed on to the kidneys for elimination (page 437). At periods of active uptake of nutritive materials by the cells the movement of water is in the reverse direction.

Eliminative Processes Make Water Intake Necessary.—In man, as in most higher organisms, both the elimination of nitrogenous waste products and the regulation of temperature are carried on by means that involve loss of water from the body. Except in a very few forms the quantities of water lost in the course of these activities are much in excess of the water of metabolism, hence to maintain the optimum water content of the body considerable amounts must be taken directly. Many foodstuffs of common consumption, including practically all fruits and vegetables, both fresh and canned, and most kinds of fresh meat, consist of more than 50 per cent water. The amount taken in daily in the food may equal or even exceed that taken specifically as drink. Representative average figures (Rowntree) give: For water of metabolism 400 gm.; for water in food 800 gm.; for beverage water 800 gm.

Stimulus to Water Intake. Should the intake of water lag behind the outgo, so that the total quantity in the body begins to fall, the strong tendency of the blood volume to remain constant, together with the limited capacity of the intercellular spaces to vary in content, leads to a depletion of the cells of some of their free water. Before this depletion gets seriously under way, and long before there is any threat to the integrity of the cells, a stimulus to additional intake in the form of the sense of thirst becomes operative (page 391), arousing the organism to as strong measures as necessary to bring about renewal of the supply. Under ordinary conditions of free access to water the ingestion is nearly always more copious than just balances the depletion, hence after the cells are restored

to normal a surplus remains tending to increase blood volume, but prevented from doing so in part by a temporary deposition of much of the surplus in the subcutaneous spaces (Skelton) and in part by an augmentation of kidney activity, which until the excess is removed eliminates water more rapidly than usual (page 437).

Effects of Deprivation of Water.—When liquid cannot be obtained, as in shipwreck, or in persons lost in the desert, bodily suffering becomes extreme, leading often to insanity, prior to death. Although thirst begins to be pronounced while the actual loss of water is still relatively slight, measurements on experimental animals show that about 10 per cent of the total amount of water in the body may be lost before serious disorders ensue. The loss of 20 to 22 per cent results in death (Rubner).

Water Intoxication.—Whenever the total quantity of water in the body exceeds the optimum, discharge through the kidneys is augmented as pointed out above. This can be prevented by the administration of pituitary extract (page 206). If after such administration large quantities of water are given, the water content of the cells is forced above the normal level. The body can be flooded without preliminary dosage with pituitary extract by introducing large quantities of water directly into the stomach by a stomach tube. In either case the passing of a certain limit of water content (in one experiment of Rowntree about 10 per cent above normal), results in symptoms described as "water intoxication," including nausea, convulsions, and stupor; in experimental animals death ensues if water administration is further prolonged. The extreme range of variation in water content that the cells of the human body can endure is thus seen to be from about 10 per cent above to about 20 per cent below normal. Some cells, particularly of the receptor and nervous systems, begin to be affected adversely long before these extremes are reached, as shown by the thirst that develops early in water deprivation, as well as by the mental aberration accompanying pronounced water loss.

HYDROGEN-ION CONCENTRATION.

In recent years hydrogen-ion concentration has been shown to be of very great significance as a factor in cell environment. The most important reasoning leading to this conclusion has already been presented (page 24); it is reviewed here briefly in introducing the present topic. The organization of protoplasm as a micellar system, in which the Donnan equilibrium prevails, implies the presence of non-diffusible ions. These appear to be chiefly anions of proteinates and phosphatides; they occur in relative amounts determined by the hydrogen-ion concentration; the further this is away from the isoelectric points of the respective compounds (on

the alkaline side), the greater the proportional conversion of proteins into proteinates, and of phosphatides into the corresponding phosphatide salts. The fundamental determining factor on which the character of micellæ, and so of protoplasm itself, depends, is conceived to be the relative proportion of non-diffusible ions, which hinges, in turn on the hydrogen-ion concentration.

Any change in hydrogen-ion concentration will thus tend to bring about an alteration in the organization of protoplasm. Since the cell membranes also show the Donnan equilibrium the same reasoning applies to them, and they may be supposed to be altered in character by changes in hydrogen-ion concentration. Direct observation shows that most cells and body fluids are nearly neutral; a pH around 7.4 represents the value commonly found. Slight changes are well endured, but it has already been pointed out (page 25) that the extreme limits compatible with life are narrow. The human body has an even narrower toleration on the acid side than that given for living things in general; it is doubtful whether human tissues can survive acidities represented by pH values as low as 6.7. It is generally recognized that death is almost sure to follow the attainment in the blood of a pH of 6.9.

The Neutrality Preserving Mechanism.—Metabolic processes tend invariably to change the hydrogen-ion concentration of the cells, and practically always in the acid direction. This is chiefly because the commonest reaction in metabolism is oxidation, leading to carbonic acid production, although other acid-producing reactions also occur (page 234). Materials taken into the body as food are likewise apt to furnish either more acid or more alkali than the optimum for protoplasm. In the face of all these tendencies toward departure from the narrow range favorable to the proper functioning of cells, it is interesting to note that the hydrogen-ion concentration of the cells and fluids of the body remains nearly constant in health. It is kept so through the operation of a mechanism that is partly physiological, and partly a matter of chemical equilibria among various substances, some of which are produced in metabolism, others always present through being included in the food. The arrangement as a whole constitutes the *neutrality-preserving* mechanism. An account of it follows.

In beginning the description it is to be noted that neutrality regulation presents two distinct phases: The first has to do with the immediate process of holding the hydrogen-ion concentration near the optimum level within the cells where acid is being produced by metabolism, and directly outside them in the surrounding tissue fluids where diffusion will carry the acids almost at once; the second deals with the larger problem of so regulating the elimination of acids and bases from the body through the channels of excretion that the balance between the two will be preserved, not merely from hour to hour, but actually from moment to moment.

The *effective* acidity of any solution, in contrast with the *titrable* acidity, depends on the hydrogen-ion concentration of the acids present; this, in turn is determined by the degree to which they are dissociated. The measure of dissociation is the *dissociation constant,* designated by K. Under the law of mass action, the expression for acid dissociation is $K \times HA \rightleftarrows H^{\cdot} \times A'$ (1). In this equation HA stands for any acid which dissociates into cations $H^{\cdot}$ and anions A'. The above equation may be written thus: $H^{\cdot} \rightleftarrows \frac{K \times HA}{A'}$ (2). From it in this form we see that the actual hydrogen-ion concentration (commonly designated as c_H) equals the product of the undissociated acid times the constant, divided by the concentration of anions. The value of K for carbonic acid is very small, *i. e.*, 3×10^{-7}. It follows that in a solution of this acid in pure water there will be relatively few hydrogen ions, as compared with a strongly dissociated acid like HCl, and equally few HCO_3' anions.

Sodium bicarbonate present in body cells and fluids is a salt which follows the rule, common to salts, of dissociating strongly. As found in the body it is about 80 per cent dissociated into cations $Na^{\cdot}$ and anions HCO_3'. These anions are the same as are produced when carbonic acid itself dissociates. If we add carbonic acid to a solution containing sodium bicarbonate we are bringing it, therefore, into a medium already rich in HCO_3' ions. Rewriting equation (2) above to apply to carbonic acid, we have $H^{\cdot} \rightleftarrows \frac{K \times H_2CO_3}{HCO_3'}$ (3) In pure solutions of carbonic acid in water the anions in the denominator of the right-hand member are so few, on account of the slight dissociation, that they affect the value of the fraction comparatively little. When sodium bicarbonate is also present, however, the number of HCO_3' anions is relatively enormous; they necessarily play their part in determining the equilibrium of the system as a whole; consequently the value of the denominator in equation (3) is greatly increased, and the value of the fraction as a whole correspondingly decreased. Since the hydrogen-ion concentration is determined by the value of the fraction it must be very much less under these conditions than when the acid is dissolved in pure water.

Buffer Action.—The effect of sodium bicarbonate in decreasing the dissociation of carbonic acid in a solution in which both are present is a particular case of a general action known as buffer action. Any chemical or physico-chemical system in which the hydrogen-ion concentration is nearer neutrality than it would be in a solution of the same amount of the same acid or alkali in pure water is a "buffered" system. There are a number of ways in which buffer effects can be produced. The method operating in the example here given applies to any situation in which there is present a salt

either of a strong base with a weak acid or of a weak base with a strong acid. The salt is not necessarily that of the acid whose CH is to be buffered. Strong acids like HCl are buffered by salts in either of the above categories. An analysis of equilibria in solutions, which space does not permit to be presented here, shows that these facts must hold. The reader is referred to detailed treatises for further information. (See bibliography at end of chapter.) Different buffers differ, naturally, in effectiveness. It is exceedingly interesting, as pointed out by L. J. Henderson, that two of the most efficient buffer systems known in chemistry, *i. e.*, carbonic acid-bicarbonate and mono-di-basic phosphate, are the buffers most abundant in cells and tissue fluids, and most important in preserving neutrality within them (this statement does not hold for blood; page 165).

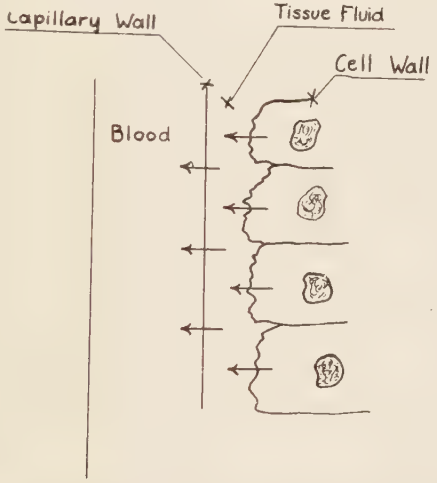

FIG. 21.—Diagram to illustrate dialysis relationships between cells, tissue fluid and blood. Arrows indicate direction of dialysis of acids The membranes through which dialysis occurs are also indicated.

The metabolic processes in the cells give rise to carbonic acid ($CO_2 + H_2O = H_2CO_3$), and alternatively to lactic and other "fixed" acids whenever the oxygen supply lags or the metabolism is otherwise abnormal. These acids enter into equilibrium relations with the carbonates and phosphates in the cells, the resultant buffering preventing the hydrogen-ion concentration from changing except slightly. The blood has a large capacity for acid (see below), with the effect that acid does not accumulate to any extent either in the tissue fluids or in the cells themselves, accumulation being prevented by the free dialysis of acid from cells to tissue fluids and from tissue fluids to blood. The diffusion relationships are indicated in the accompanying diagram (Fig. 21). The same buffers as are in

the cells occur also in the intercellular tissue fluids; these are accordingly as little affected in respect to hydrogen-ion concentration by the entry of acid into them from the cells as are the cells by the production of the same acid inside themselves as the result of metabolism. From the tissue fluids the acids dialyze into the blood. Here they encounter a second buffer mechanism much more effective than the one in cells and tissue fluids on account of its much larger capacity for acid.

That there is a limit to the effective buffering action of bicarbonate or of a phosphate mixture becomes clear from a further study of equation (3) above. That equation shows the CH of a solution containing bicarbonate to be less than of an equivalent amount of acid in pure water. It also shows, however, that the CH must increase steadily as the amount of acid increases. The *undissociated acid* is a factor in the numerator of the fraction, and the value of the fraction must increase in direct proportion as its numerator increases. In this type of buffering the CH is not held, therefore, absolutely uniform, it merely increases very slowly as acid is added. Evidently the addition of considerable amounts of acid might bring on an increase in CH harmful to living tissues.

Buffer Action of Blood.—In the blood two effects coöperate to keep the CH from rising, even though acid may be entering rapidly from the tissue fluids. The respiratory pigment, *oxyhemoglobin* (page 215), gives up oxygen during the time the blood is passing through the tissue capillaries (page 218), which is exactly the time when the blood is taking up carbonic or other acid from the cells and tissue spaces. In giving up oxygen the pigment changes from oxyhemoglobin to reduced hemoglobin. Under the conditions obtaining in blood the former compound is more acid than the latter; there is accordingly a tendency for the blood to decrease in CH at exactly the instant acid is entering it from the tissues. In counteracting this tendency a good deal of acid is taken care of. The second, and about equally effective, means of taking up acid without much change in CH depends on the interaction of several factors, and will have to be described in some detail. First is to be noted that blood contains abundant NaCl which will react with H_2CO_3 according to the formula: $NaCl + H_2CO_3 \rightleftarrows NaHCO_3 + HCl$ (4). This reaction cannot proceed very far unless some one of the products is removed from the system, and will be of no importance in keeping down the CH unless the removed product is HCl. As a matter of fact there is active removal of HCl, which removal forms the basis for this part of the buffer mechanism of blood. The HCl passes out of the system by migrating into the red corpuscles (page 217). The migration is apparently in large part a manifestation of the Donnan equilibrium (page 27), the relationship of diffusible ions being such that any production of HCl in the blood

will lead to a migration of much of it into the corpuscles. The effect is to make the CH of the corpuscles higher than of the liquid part of the blood, *i. e.*, the plasma. More HCl enters the corpuscles, however, than can be accounted for by the simple difference in CH between them and the plasma, and we must suppose the corpuscles to contain available bases by which the surplus acid is neutralized. These are usually considered to be provided by the hemoglobin of the corpuscles. This action is not to be confused, however, with the effect of hemoglobin in changing CH as it gives off oxygen; that is an independent process. Hemoglobin enters actively, as we thus see, in both main methods of preserving the neutrality of blood. It is calculated to account for fully 80 per cent of all the acid the blood ordinarily takes up. The balance is cared for in part by the bicarbonates and phosphates, which act in blood exactly as in tissue fluids, and in part by a moderate buffer effect exerted by the proteinates present in blood plasma.

Physiological Neutrality-preserving Mechanisms.—In the paragraphs above that phase of the neutrality-preserving mechanism which is primarily a matter of chemical equilibria has been outlined. There remains a part which is mainly physiological. This can be discussed here only in general terms, since its adequate presentation includes much matter not yet dealt with, which forms the substance of later chapters. The first step consists in the removal of that portion of blood which has been in the capillaries in diffusion relations with the tissue fluids (see Fig. 21) and its replacement with other blood, less charged with acid. This is done by the circulation, which is so adjusted that no given sample of blood is in diffusion relations with tissue fluids for more than two or three seconds at the most before being swept on out of the capillaries into the veins, and thence to the organs of excretion, the lungs and kidneys.

The lungs are discussed in detail in Chapter XXIII; here it is to be noted merely that as the blood passes through the pulmonary capillaries gaseous carbon dioxide dialyzes out from the blood into the air of the pulmonary alveoli. The significance of this process is that it gets rid of carbonic acid without any corresponding loss of base, and thus serves to relieve the buffers of the blood of their charge of acid, and to restore them to their former acid-holding capacity.

Elimination of "Fixed" Acids.—So-called "fixed" acids, which are acids other than carbonic produced in metabolism, and include some sulphuric and phosphoric acid from the metabolism of proteins and phosphatides, as well as various organic acids, invariably react with sodium bicarbonate to produce the corresponding acid salt and an equivalent amount of carbonic acid. This latter will react with sodium chloride, according to reaction (4) (page 164),

provided the capacity of the corpuscles to take up hydrochloric acid has not been exhausted. This reaction produces more sodium bicarbonate to replace that lost in the neutralization of the "fixed acids, and leaves the CH of the blood virtually where it was before. The sodium salts of the "fixed" acids pass in the blood to the kidneys where there is a reaction with ammonia produced by the kidney cells (page 148), with the formation of ammonium salts of the acids, and return of the sodium to the blood. By this reaction with ammonia the acids are eliminated as neutral salts without depleting the blood of its store of useful base. Not all the acid eliminated by the kidney is in combination with ammonia; some passes out as acid, raising the hydrogen-ion concentration of the urine, which is normally more acid than blood, ranging in health between about PH 4.8 and PH 7.4.

The relative volume of acid eliminated by the kidneys and lungs respectively may be as much as 1 to 200. If stated as normal solutions average figures give about 150 ml. fixed acid discharged from the kidneys per day, as contrasted with 30,000 ml. carbonic acid, more or less, expelled from the lungs as gaseous carbon dioxide in the same time. This difference is to be expected in view of the fact that CO_2-producing reactions make up the great bulk of metabolism.

Elimination of Excess Base.—From the account as given thus far there would appear to be little tendency for the supply of base to become so excessive as to call into action a special mechanism for elimination of the surplus. The first effect of an increase in the amount of alkali in the body is to relieve the bases within the red corpuscles of the necessity of combining with all the HCl set free in reaction (4). Only after this action has gone so far that bases within the corpuscles are in excess does there begin to be a corresponding excess of base in the plasma. Excess can be obtained experimentally by direct administration of considerable amounts of sodium bicarbonate. Such treatment is followed by appearance of bicarbonate in the urine, suggesting simple excretion. In extreme cases the urine may become alkaline to a PH of about 8, showing that much of the excess base is eliminated as such, and not in combination with an acid as a neutral salt (see also page 233).

Normal Reaction of Blood and Tissues.—The fact has already been brought out that the usual reaction of blood and tissues is approximately PH 7.4, *i. e.*, slightly on the alkaline side of strict neutrality. This is due chiefly to the presence of sodium bicarbonate. The equilibrium leading to a slight excess of OH' ions may be pictured simply as follows:

$$\begin{aligned} NaHCO_3 &\rightleftarrows Na^{\cdot} + HCO_3' \\ H_2O &\rightleftarrows H^{\cdot} + OH' \\ H^{\cdot} + HCO_3' &\rightleftarrows H_2CO_3 \\ Na^{\cdot} + OH' &\rightleftarrows NaOH \end{aligned}$$

The dissociation of water yields hydrogen and OH′ ions which react with the products of dissociation of $NaHCO_3$, forming slightly dissociated H_2CO_3 and strongly dissociated NaOH. This difference in degree of dissociation brings about a surplus of OH′ ions, and consequently a reaction on the alkaline side of neutrality. The exact CH depends on the ratio of H_2CO_3 to $NaHCO_3$, as indicated in the equation:

$$CH = \frac{K \times H_2CO_3}{NaHCO_3}$$

Acidosis and the Alkali Reserve.—The above equation shows that the total quantity of bicarbonate present in the blood must be a factor in determining its CH. We have already seen that reaction (4) (page 164) determines the amount of bicarbonate in the blood up to a limit set by the capacity of red corpuscles to take up HCl and by the action of the lungs and kidneys in eliminating carbon dioxide and fixed acids respectively. Should the production of fixed acids be so greatly augmented as to exceed the ability of the kidney to eliminate them (as in the disturbed metabolism of diabetes; page 235), or should the kidney itself become impaired in acid-excreting power the concentration of sodium salts of fixed acids in the blood necessarily increases, with corresponding displacement of carbonic acid from bicarbonate. Through the operation of reaction (4) additional bicarbonate will be formed, however, up to the limit of the power of red corpuscles to take up HCl. Thereafter, if fixed acids continue to accumulate there will necessarily be a decline in bicarbonate concentration, as the fixed acids continue to form sodium salts at its expense. The result will be a shift of blood hydrogen-ion concentration toward the neutral point or even beyond it on the acid side. This situation is known as *acidosis*. It is measured by comparing the amount of bicarbonate in the given blood with the normal. The expression *alkali reserve* is used to designate the amount of bicarbonate present. It is valuable as indicating how much more acid production may occur before a dangerous hydrogen-ion concentration (about PH 6.9; page 161) will be reached. In the strict sense the alkali reserve includes the sum total of available base, in corpuscles as well as plasma; restriction of the term to bicarbonate is a convention which should be used only in full understanding of its meaning.

Summary.

The cells and their liquid environment constitute an equilibrium system of such a sort that changes in either affect the other. An environment favorable to cell life and cell function is normal; one that threatens life or disturbs function is abnormal.

Neglecting intrinsic and inevitable metabolic changes leading to senility we may accept the following general proposition: *If ideal cell environment could be maintained continuously about every cell in the body they would all continue to function correctly and normal healthy life would go on indefinitely.*

In view of the above an important part of the task of Physiology is that of determining what are the factors that constitute suitable cell environment; the limits of variation in each within which normal metabolism can go on; how metabolism itself affects the environment; and how, in the complex body of man, the various cells and groups of cells act to maintain or modify the environment of one another.

The following environmental factors are listed: (*a*) Temperature; (*b*) water content; (*c*) hydrogen-ion concentration; (*d*) inorganic salts; (*e*) nutrients; (*f*) vitamins; (*g*) miscellaneous dietary constituents; (*h*) hormones; (*i*) bacterial toxins and immune substances; (*k*) oxygen; (*l*) miscellaneous metabolites; (*m*) various external energy effects.

The extreme temperature range compatible with life in dried spores is from a few degrees above absolute zero to about 20° C. above the boiling-point of water. In cold-blooded animals, and in resistant individual tissues in warm-blooded animals the range is from about 0° C. to 43° to 46° C.

The average temperature of the human body is 37° C., with a daily range of about 0.5° on each side of the average. If the temperature is as much as 2° C. away from the average for more than a few minutes definite symptoms develop, indicating that the environment is unfavorable. The extreme range compatible with life in man is from about 25° to about 44° C.

Rise in temperature quickens bodily processes. The optimum temperature is that at which the quickening effect just fails to be counteracted by the destruction due to too high a temperature. The normal temperature of warm-blooded animals falls very near this optimum, being kept so through the operation of an automatic heat-regulating mechanism.

In cold-blooded animals and in excised warm-blooded tissues changes of temperature are accompanied by changes in velocity of metabolic processes. The temperature coefficients of physiological processes are usually somewhere near 2, indicating that they are in part physical and in part chemical.

Metabolic activities generally produce heat. This is transferred from the cells in which it is produced to the immediate environment. The further transfer, either to other cells or to the exterior, involves the operation of the heat-regulating mechanism, to be discussed in Chapter XXVIII.

Water content is important in that nearly 75 per cent of protoplasm is water; also in that water is the vehicle by which cells receive and discharge materials. Water is derived either from the exterior or is set free within the cells as water of metabolism.

The estimated distribution of water in the body (for a 70-kg. man) is: Protoplasmic water, 30 kilos; in bones and other hard structures, 2.5 kilos; blood plasma, 2 kilos; intercellular liquid and serous spaces, 7.5 kilos. The significant points about these figures are the relatively small bulk of liquid serving as cell environment and of liquid available as a vehicle for the transport of the materials within the body.

The setting free of water of metabolism tends to raise the water content of the cells above the optimum, with the result that the cells expel water. Since the capacity of tissue spaces and blood channels is limited, this water is necessarily passed on promptly to the organs of elimination. The cells regain the water thus lost by their uptake of hydrated nutritive molecules.

Both nitrogenous waste products and excess heat are eliminated by means involving loss of water. Water of metabolism is insufficient in most forms, hence additional water must be ingested. A representative estimate for one day is: Water of metabolism, 400 gm.; water in food, 800 gm.; beverage water, 800 gm.

Blood volume tends to remain constant; also the tissue spaces have very limited capacity to vary in content; hence loss of water from the blood through the channels of elimination, in excess of water of metabolism, depletes the cells somewhat, arousing thirst and leading to active measures for ingestion of water.

When water is unobtainable bodily disturbances come on as water loss continues, becoming serious after about 10 per cent of the total amount of water in the body is lost, and culminating fatally in experimental animals after loss of 20 to 22 per cent.

An increase in water volume amounting to about 10 per cent is followed by symptoms of "water intoxication," and by death if administration of water is continued.

Hydrogen-ion concentration is important as a factor in cell environment since the intrinsic organization of protoplasm varies with every change in C_H. Most cells and fluids of the human body have hydrogen-ion concentration represented by about p_H 7.4. Only comparatively slight variations from this value can be borne. Death is apt to follow the attainment in human blood of p_H 6.9.

Metabolic processes tend generally to change the hydrogen-ion concentration in the acid direction, chiefly through the production of CO_2, but in part through the formation of "fixed" acids. The tendency is prevented from proceeding to a harmful degree through the operation of a *neutrality-preserving* mechanism, partly a matter of chemical equilibria and partly physiological.

Neutrality regulation has two phases: The first is concerned with preventing undue changes in c_H within the cells and in the immediately surrounding fluids; the second with regulating the elimination of acids and bases through the channels of excretion in a manner that will preserve a balance between them.

Within the cells c_H is held nearly constant through the presence of bicarbonate and of a mixture of mono and dibasic phosphates, acting as *buffers*. This action depends on the fact that in the mass-law expression for the dissociation of an acid the fractional term which is in equilibrium with c_H has anions in the denominator. When a strongly dissociated salt of a strong base with a weak acid, or of a weak base with a strong acid, is present in the system there is a great increase in number of anions, a corresponding increase in the value of the denominator, and hence a marked decrease in the value of the fraction as a whole, *i. e.*, the c_H.

The blood has a much greater capacity for acid than have either cells or tissue fluids. The result is that acids tend to dialyze rapidly from cells through tissue fluids to the blood. Two factors coöperate to bring about this large capacity. In the first place, *oxyhemoglobin*, present in arterial blood, is more acid than *reduced hemoglobin*. The change from the former to the latter takes place exactly when and where carbonic and other acids are entering the blood from the tissues; thus much acid can be taken up without more than restoring the former c_H. In the second place red corpuscles have a considerable capacity for taking up and neutralizing HCl. This acid is formed in the reaction: $H_2CO_3 + NaCl = NaHCO_3 + HCl$. By this action about as much acid is cared for with little or no change in c_H, as by the conversion of oxyhemoglobin to reduced hemoglobin.

The physiological part of the neutrality-preserving mechanism includes the rapid removal of acid-bearing blood and its replacement with less acid blood, by means of the circulation; the action of the lungs in eliminating carbonic acid as gaseous carbon dioxide; the action of the kidneys in eliminating "fixed" acids. In this latter action bases are conserved, in part through a higher c_H of urine than of blood and in part through the property of the kidney of producing ammonia, which combines with the acids and restores the more valuable bases to the blood.

When excess of base occurs in the body there is direct excretion of base from the kidney, lowering the c_H of urine, sometimes to a pH value of around 8.

The usual reaction of blood and tissues (around a pH of 7.4) depends chiefly on the presence of bicarbonates, and the actual c_H is a function of the ratio of carbonic acid to bicarbonate. Should the production of fixed acids exceed the ability of the kidney to eliminate them the reaction between fixed acids and bicarbonate

will ultimately outstrip the ability of the buffer system as a whole to maintain the normal bicarbonate concentration; there will be a decrease in the amount of this substance in the blood, with a corresponding increase in CH. This situation is known as *acidosis*. Its degree may be measured in terms of bicarbonate concentration, as compared with the normal. Hence the custom has arisen of calling the bicarbonate concentration, the *alkali reserve*.

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CHAPTER XI.

CELL ENVIRONMENT: INORGANIC SALTS; NUTRIENTS.

INORGANIC SALTS ESSENTIAL TO PROTOPLASM.

That inorganic salts play important roles in the economy of protoplasm has already been pointed out (pages 24 and 37). Their presence inside the cells implies their simultaneous presence in the surrounding tissue fluids. Salts are the main, but not the only, factor in maintaining osmotic and Donnan equilibrium between cells and body fluids (page 32).

The interesting fact has already been mentioned (page 37) that the salts found in the body fluids of most animals, including man, are the same as predominate in sea water, and with the exception of magnesium in the same proportion, although only about one-fourth as concentrated. We know of no fundamental reason why this should be so; various individuals have suggested it to mean that the ocean at the close of the Cambrian period, when some animals began to forsake the sea to take up life on land, had the proportion and concentration of salts now present in body fluids, and that the animals that took to the land simply brought with them the salt mixture by which they had been surrounded, and to which their protoplasm was necessarily adjusted.

While the cells are in equilibrium with the tissue fluids surrounding them, their precise saline contents are quite different. Thus potassium salts are about four times as abundant as sodium salts within muscle cells (K = 3.20 parts per 1000; Na = 0.80 parts per 1000; Katz), while in the body fluids sodium is more than ten times as concentrated as potassium (Na = 3.40 parts per 1000; K = 0.31 parts per 1000; Carl Schmidt). The maintenance of this difference is presumably due chiefly to the Donnan equilibrium, which counteracts the tendency of ions to distribute themselves uniformly throughout a system (page 27).

Sodium Chloride Equilibrium.—The human body is estimated to contain 100 to 120 gm. sodium chloride, 40 to 50 per cent of which is in solution in blood and tissue fluids, the balance incorporated in living protoplasm. The daily intake is quite variable, being dictated as to quantity more by the use of salt as a seasoning for food than by actual physiological need. The usual range is between 5 and 20 gm. daily. The loss by excretion balances the intake in the long run, although the two do not always keep even pace.

Slight variations in intake are balanced promptly by corresponding variations in elimination, but when the intake is markedly increased or diminished the adjustment of outgo lags behind (sometimes for as much as three days). This lag does not result in changes in the sodium chloride concentration of the blood, except very transiently when the intake is markedly *increased*. Under this condition the salt concentration rises considerably at first (the rise is mitigated in part by an uptake of additional water from the tissues due to the heightened osmotic pressure of the blood, leading to *plethora* of the latter), but soon returns to normal as the result of deposition of the salt in the tissues, especially the skin (Patdberg). The deposit is not permanent; after the lag in adjustment is overcome the elimination exceeds the intake until the deposited salt is got rid of. During a period of excess elimination the sodium chloride concentration of the blood is not demonstrably higher than normal; we are consequently at a loss to explain the escape of more sodium chloride through the kidneys at such times than at others when no extra store of the salt is in the tissues.

A marked *decrease* in salt intake is followed after a short lag by a diminution in salt elimination. If one simply discontinues taking salt altogether the daily elimination declines in about four days from its initial level to a new one in which the loss is almost negligible (0.2 to 0.3 gm.). Hand in hand with this small loss goes a reduction in water content of the body, keeping the osmotic relations constant. If instead of merely leaving salt out of the diet, one undertakes a regimé of complete starvation, the salt elimination is on a somewhat larger scale, inasmuch as the wasting of the body tissues sets a small amount of salt free which must be discharged in order to keep the osmotic pressure of the tissue fluids from rising.

The facts of salt starvation just described show that large salt elimination is not a necessary part of kidney action, and justify the conclusion that the salt intake might be greatly reduced without harm. As a matter of fact, carnivorous animals, and human races, like the Eskimos, also virtually carnivorous, experience no particular craving for salt, and take none except incidentally in the flesh foods eaten. The quantities thus obtained balance all inevitable losses. Herbivorous animals, on the other hand, and man on a mixed diet, experience a definite craving for salt, which appears to be based on a real physiological need for larger quantities than the food ordinarily affords. The explanation suggested by Bunge is that in the presence of large quantities of potassium salts undergoing elimination the kidneys eliminate more sodium than they would otherwise. Certain vegetables, notably potatoes, and the grasses on which grazing animals habitually feed, are particularly rich in potassium salts. When these are in the diet sodium will be eliminated to excess, calling for an equivalently increased

intake to make good the loss. The kidney condition leading to such an augmented excretion of sodium salts is not yet understood.

The Calcium Balance. –The normal concentration of calcium salts in blood is uniform and small (0.12 parts calcium in 1000 parts blood plasma; Carl Schmidt). The body, as a whole, contains more lime than any other inorganic material, on account of the high calcium phosphate content of bones. The total amount of lime salts is estimated to be 2 per cent of the body weight. An average of about 0.45 gm. calcium (equivalent to 1.2 gm. $Ca_3(PO_4)_2$) is eliminated daily from the body of an adult on a diet containing a minimum of lime. The main channel of elimination is from the large intestine in the feces, although the urine normally contains small quantities of lime salts. The average intake exceeds the above figure by about 50 per cent; the intake itself varies according to the quantity of milk ingested, this being the food richest in lime of all common dietary constituents. In adults the elimination balances the intake under ordinary conditions. In growing children, on the other hand, calcium is continuously being deposited in the bones, hence the intake regularly exceeds the outgo. Studies on growing children indicate that between 0.2 and 0.4 gm. calcium are deposited daily on the average throughout the whole period of active growth, *i. e.*, from late infancy to about the fourteenth year. Obviously the diet of growing children should contain at least twice as much lime as the minimum sufficient for adults.

An interesting illustration of the maintenance of calcium equilibrium as between blood and tissues is seen in connection with the production of milk in lactating animals. Such animals, even though fed a diet apparently ample in lime, commonly supply to their milk greater quantities of calcium than they assimilate from the diet. Meanwhile the calcium concentration of the blood remains normal. The excess calcium has been shown to be provided at the expense of the store of lime in the bones. While this store is chiefly in the form of nearly insoluble calcium phosphate it nevertheless is in equilibrium relations with the calcium salts of the body fluids, so that when the latter begin to show signs of falling off enough lime compound will reënter solution from the bones to make good any loss. The same phenomenon is a usual accompaniment of child-bearing in women when lime must be provided for bone formation in the developing fetus. It is the basis for the popular saying that each child costs the mother a tooth, the tendency to loosening of the teeth being due to the general softening of the bones following a decrease in their lime content. The actual regulation of equilibrium between blood calcium, bone calcium and food calcium appears to be a function of the recently discovered hormone of the parathyroid glands. (For an account of this hormone and its action see Chapter XII.)

Potassium Salts.—Little specific information is available regarding the role of potassium. It occurs in blood in somewhat higher

concentration than calcium (0.3 parts potassium in 1000 parts plasma; Carl Schmidt). The maintenance of a definite blood concentration is thought to be important, particularly in connection with the optimum salt environment for tissues (page 37). The intake varies widely, according to the diet, and on account of the high potash content of common vegetables is apt to be considerably larger than of any other inorganic constituents except sodium, which is taken deliberately. The kidney cells appear to excrete potassium positively (page 147), hence the maintenance of uniform blood content can be attributed to the action of the kidneys.

Iron and Iodine Salts.—Salts of rather special interest are those of iron and of iodine, which play roles in connection with individual substances, rather than with protoplasm in general. *Iron* is an essential constituent of hemoglobin (page 215). It is lost continuously, although slowly, from the body and must be, therefore, regularly included in the diet. Fortunately most foods of animal origin and commonly used fruits, cereals and vegetables as well, contain iron in moderate concentration. Failures in iron metabolism are more frequently due to disorder of the blood-forming tissues than to shortage of the metal in the diet.

Iodine is a constituent of the hormone of the thyroid gland (page 198) and hence must be available in the diet. The wastage from the body is on a very small scale, so only a little dietary iodine is required. The substance occurs in Nature chiefly in exceedingly dilute solution in sea water. Within recent years it has been shown that there is apparently a definite relation between the incidence in the population of disorders due to thyroid deficiency and the natural occurrence of iodine in the food. Iodine salts are exceedingly soluble, and the cultivation of the soil leads in a few years to the washing out of any iodine compounds that may have been present prior to settlement. The result is that in most regions remote from the sea, and so cut off from the possibility of receiving iodine in wind-blown spray, both plants and the animals that feed on them are likely to contain very little iodine; animals less than proper functioning demands. Commercial table salt is virtually iodine-free as ordinarily refined, but of late years experiments have been tried of adding minute amounts of sodium iodide to table salt at the refineries. The results have been generally encouraging, as indicating a simple and practical method of supplying the human population with the needed iodine.

NUTRIENTS.

The nutrients as factors in cell environment are significant as the sole source of protoplasm-building and energy-yielding compounds. Fortunately for convenience of description the highly diverse foodstuffs which compose the usual organic diet of men and animals

contain only three kinds of nutrients, carbohydrates, proteins and fats. These, in turn, are reduced by digestion to just three simple categories—carbohydrates to glucose (levulose and galactose also in small amounts (page 178); proteins to amino-acids and fats to fatty acids and glycerol (Chapter XXV). The latter are resynthesized into fats again during absorption. All these products pass from the digestive tract into the blood at times and in amounts determined by the consumption of food by the individual and by the activity of the digestive process. When the whole intake of food for the day is in three meals, as is the habit of most Americans, there are three periods of active absorption, following the meals, during which the concentration of digested food products increases in the blood. Throughout the remaining time there is a decline, either actual or potential, in the concentration of these materials, as they dialyze from the blood through the tissue fluids into the cells. The constant using up of the compounds in cell metabolism maintains a diffusion gradient from tissue fluids to cells which insures dialysis so long as the blood continues to have a supply.

Glucose in Blood and Tissue Fluids.—Certain features connected with the maintenance of supplies of nutrients in the cell environment differ with the different foods; it will accordingly be necessary to consider each by itself. Glucose is, as already pointed out (page 52), the great energy-yielding cell food, being looked upon at present as probably the only directly oxidizable food constituent (page 185), and making up two-thirds more or less of the entire food supply on which the cells draw for their metabolic needs. It occurs in the blood and tissue fluids in health in concentration of 0.10 to 0.12 per cent, never exceeding 0.17 per cent, except transiently. This limit of concentration could not be overstepped, as a matter of fact, except on a very wasteful basis, because it is the threshold limit for kidney reabsorption (page 435), and if glucose were to be in the blood in excess of this concentration there would be elimination of the substance in the urine.

Glycemia and Glycosuria. The presence in the blood of sugar in greater than normal concentration, *i. e.*, in excess of 0.12 per cent, constitutes the condition known as *glycemia* (*hyperglycemia*, according to many authors). If the glycemia becomes so intense that the reabsorption limit of the kidney is passed, and sugar appears in the urine in appreciable quantity, we have the condition of *glycosuria*. It should be noted that sugar in the urine, from any cause whatsoever, constitutes glycosuria. Disaccharides, such as cane sugar, are not normal constituents of the blood, and if introduced into it are eliminated completely by the kidneys. Either the disaccharides are secreted actively by the tubule cells in the manner pictured for uric acid and urea (page 147), or they simply filter out through the capsular membranes along with the other

filterable constituents and escape reabsorption completely. Disaccharides in the blood will thus cause a glycosuria without there being necessarily an antecedent glycemia, but there will be no glycosuria due to glucose except as the result of glycemia exceeding 0.17 per cent, provided the kidneys are functioning normally.

Tolerance for Glucose.—The body tissues use glucose continuously at a rate which varies from a minimum, when the only metabolism going on is basic metabolism (page 59), to a maximum when the tissues are as active as they can be. In addition to this use of glucose in metabolism the muscles have the property of storing certain quantities in the form of glycogen (pages 80 and 89) and the liver has the same property (see below). Glucose is converted into fat and stored in the adipose tissues under certain conditions (page 188). If the rate at which glucose is supplied to the blood does not exceed the combined rate of utilization and storage there will be no tendency for the sugar concentration of the blood to rise. If, on the other hand, glucose is introduced more rapidly than it can be handled in one or the other of the above ways the sugar concentration is bound to rise, bringing on first glycemia and then glycosuria. Direct experiments in which glucose is introduced into the blood intravenously have shown that in rabbits and dogs, and in man, about 0.8 gm. of glucose per kilogram body weight can be introduced each hour, without inducing any glycosuria (Woodyatt and co-workers). If larger amounts are injected sugar appears in the urine, although not all the surplus is thus lost to the body. Part can still be stored as glycogen or fat. If the hourly input exceeds 2 gm. glucose for each kilogram of body weight virtually the whole of the excess is given off in the urine.

Glycogenic Function of the Liver and Muscles.—The quantities of glucose absorbed from the digestive tract into the blood after an ordinary meal are enough to raise the concentration in blood well above the limit of 0.17 per cent. That the concentration does not actually rise above this level is due to the "glycogenic function" of the liver, discovered by Claude Bernard in 1848, and to the similar "glycogenic function" of the skeletal muscles, already mentioned (pages 80 and 89). What happens is that the blood draining the stomach and small intestine all passes through the portal circulation before entering the general blood stream, and in passing through the capillary channels of the liver loses a large part of its glucose to the liver cells. These cells have the very important property of converting glucose to the polysaccharide, *glycogen*, as have also the skeletal muscle cells. The change of glucose into glycogen is a type of action usually catalyzed by enzymes (page 53). Up to the present, however, no enzyme has been shown to function in the liver to this end.

The liver ordinarily contains a considerable store of glycogen.

The latter substance does not tend to diffuse out into the blood stream, but remains in the liver cells until reconverted into glucose. This reaction, namely the hydrolysis of glycogen to glucose, is catalyzed by an enzyme, *glycogenase*. It is worth nothing that the digestion of carbohydrates in the alimentary tract gives rise to three or more monosaccharides, all of which are converted into glycogen; when the latter is reconverted into sugar, on the other hand, it gives rise only to glucose. Under normal conditions, therefore, the sugar in the cell environment is almost exclusively glucose.

The Glucose-glycogen Equilibrium.—The equilibrium between blood sugar and glycogen is so adjusted as to tend to hold the sugar concentration in the blood nearly constant at about 0.12 per cent. Such evidence as we have at present indicates strongly that this equilibrium is controlled through the action of insulin, the hormone secreted by the islands of Langerhans in the pancreas (page 203). One of the functions of insulin appears to be to put a stop to the action of glycogenase, by which the conversion of glycogen to glucose is catalyzed. Consequently, glycogen will tend to accumulate in the liver whenever the blood flowing through it contains insulin as well as sugar. But the stimulus to the island cells, causing them to pour out insulin, is thought to be the presence of sugar in the blood in concentration exceeding 0.12 per cent (Sevringhaus and Smith). Thus the rapid absorption of sugar after a meal brings into action a mechanism which puts a stop to the action of glycogenase without affecting the process by which glycogen is formed in the liver. When, between periods of absorption, blood sugar falls off, due to its use by the tissue cells in metabolism, insulin ceases to be secreted and the action of glycogenase proceeds without hindrance until the blood-sugar concentration at which insulin is discharged from the islands is again reached.

Nervous Glycemia.—Certain conditions are known in which the conversion of glycogen to glucose in the liver goes on more rapidly than the maintenance of ordinary equilibrium calls for. This action is spoken of as the "mobilization of sugar." The effect is a glycemia, since the production of sugar exceeds its utilization by the tissues. Stimulation of the great splanchnic nerves (sympathetic) is one means of inducing mobilization of sugar experimentally. The evidence indicates that there is a direct autonomic nervous effect on the liver. The nerve pathway over which the excitation passes in causing nervous glycemia either originates in or passes through a particular area of the medulla oblongata. There is a definite region of this portion of the brain whose irritation, as by a needle, causes glycemia (the so-called "piqûre" experiment). The effect cannot be obtained if the splanchnic nerves are cut. This is taken as proving that the nerve paths to the liver, by which sugar mobilization is caused, proceed from the indicated spot in the medulla and pass over the splanchnic nerves.

Adrenin Glycemia. –The great splanchnic nerves contain efferent fibers to the adrenal bodies and to various other organs, as well as to the liver. It is known that stimulation of these nerves causes an out-pouring of adrenin, the hormone produced by the adrenals (page 202). This hormone is quickly distributed to all parts of the body in the blood. Furthermore adrenin is known to be an efficient stimulus for causing the liver cells to convert glycogen to sugar. Many physiologists believe that a considerable part of the influence causing sugar mobilization which is set in play by splanchnic stimulation acts thus indirectly through the adrenals.

Sugar Mobilization a Feature of the "Emergency Reaction."—In the intact body the occasion for mobilization of sugar is exceptionally vigorous metabolism. Flooding the blood with sugar is always wasteful; from the standpoint of efficient bodily operation it is unjustifiable unless more serious consequences are thereby offset. When preservation of life or health may depend on high metabolic activity, as in the flight from pursuing danger, or the resistance of the body to extremes of cold, the greatest possible demands of the tissues for fuel may be anticipated through sugar mobilization, and thus a useful purpose served. There is direct evidence that in time of bodily stress glycemia is normally present, and usually glycosuria as well. This is one phase of an important series of adjustments by which the organism automatically fits itself to cope most effectively with immediate threats to bodily well-being. The series, as a whole, makes up the "emergency mechanism," to which our attention has been called chiefly by Cannon. The mechanism as a whole is discussed in Chapter XL, page 735.

Phlorhizin Glycosuria.—There is a poison, *phlorhizin*, which disturbs sugar metabolism in two important respects: (*a*) It affects the cells of the kidney tubules in such a way that sugar is no longer reabsorbed from the glomerular filtrate; (*b*) it interferes temporarily with the discharge of insulin from the islands of Langerhans. The result is, of course, a continuous wastage of sugar through the kidneys with a corresponding tendency for the concentration of blood sugar to fall. This is met by a continuous conversion of liver glycogen into sugar, the process continuing until the liver is nearly deprived of its store. (To cause the glycogen to disappear completely muscular exercise must be induced or the animal placed in a cool environment.)

Even after the liver has given up all its glycogen there continues to be an out-pouring of sugar from the kidneys. In case the poisoned animal is fed ample carbohydrates these will form the source of this additional sugar. If the animal has fat in its adipose tissues this will be drawn upon (page 186). A very significant fact is, however, that the loss of sugar continues, even though the animal is so starved as to have no available supplies either of glycogen or fat.

It has been proved that the source of the sugar in this event is in the body proteins, which are decomposed in such a manner as to yield a sugar residue (page 182). The mechanism for maintaining a certain percentage of sugar in the blood operates so persistently that when the ordinary sources of supply, liver glycogen and adipose tissue fat, are exhausted, the indirect source represented by the body proteins is drawn upon.

Insulin and Blood Sugar.—The disease *diabetes mellitus*, to which more definite reference will be made later (page 203), is now known to be due to a deficiency in the supply of *insulin*. A second function of this hormone, additional to the one described above, is to lower the glucose tension of the tissues (Macleod), causing them to take sugar from the blood. It follows that when insulin is deficient the tissues fail to take up sugar at their normal rate. Since sugar is the main fuel substance of the tissues, this means a serious disturbance in tissue metabolism. A deficiency in insulin is likewise apt to be attended by glycemia and glycosuria. In the diabetic, whose body is chronically short of insulin, just as in the phlorhizinized animal (see above) the insistent demand of the tissues for fuel leads to an active decomposition of tissue proteins with the formation of a sugar residue if no other source of sugar is available. Thus glycemia and glycosuria may be present, even though no carbohydrates are taken in the diet. Since the ability of the liver to retain glycogen also depends on the presence of insulin (see above) it follows that the tolerance of the body for glucose (page 177) is directly proportional to the amount of insulin present. The relationship is so significant that decrease in sugar tolerance is looked upon as an important diagnostic sign in incipient diabetes.

When an over-concentration of insulin is produced by injecting insulin directly into the blood the tissues take up sugar much more rapidly than they do normally. The immediate result is a decrease in the concentration of blood sugar. In man, when the sugar concentration falls to 0.075 per cent, *subjective* symptoms begin to develop. These consist especially of extreme hunger and sensations of fatigue. The first *objective* signs come on at a sugar concentration of about 0.06 per cent. They take the form of respiratory disturbances, together with muscular tremors and incoördination, and are seen particularly well in dogs. At about 0.031 per cent blood sugar in rabbits (Blatherwick and associates), and at somewhere near the same concentration in other mammals as well, typical convulsions occur. These consist of violent convulsive seizures lasting from thirty seconds to about one minute, alternating with periods of unconsciousness. Successive seizures are progressively less violent, and in the course of an hour or so death from respiratory failure ensues.

So far as can be judged, the symptoms which follow injection of

excess insulin into the blood are immediately due to disturbance of function in some of the cells of the central nervous system. The symptoms suggest asphyxia of these cells, but why excessive taking up of sugar into the cells, or the absence of the usual concentration of sugar from the surrounding tissue fluid, should induce asphyxia, or a state resembling it, we cannot say at present.

One of the very striking things about the situation is the prompt and complete recovery that follows subcutaneous administration of glucose. Unless the symptoms are very far advanced the injection of 2 gm. of glucose per kilogram body weight will usually bring about recovery within five minutes. If the animal is near death one-half hour or more may be required for complete restoration.

Amino-acids.—The second group of organic foodstuffs consists of the amino-acids. These are indispensable constituents of the cell environment because they alone can make good the protein losses which are a feature of basic metabolism (page 60). Food proteins are decomposed in the digestive tract into their constituent amino-acids. These are absorbed into the blood and dialyze thence into the tissue fluids in proportion to their abundance in the alimentary tract. There is a minimum concentration of amino-acids in the blood, amounting to about 5 mg. total acids per 100 ml. blood, below which there is no further dialysis. It appears that equilibrium is established at this level. During the periods of active absorption the concentration in the blood will tend to rise; between these periods it will tend to fall, until the equilibrium level noted above is reached. A fact of some importance in this connection is that the processes of basic metabolism appear to go on very uniformly from moment to moment (page 60) and quite independently of the functional metabolism. The primary use of amino-acids in restoring protein wastage is thus continuous and very uniform. Furthermore, in the human body the materials to be restored are characteristic human proteins, with proportions of amino-acids usually not the same as in the food proteins. The *utilization* of individual amino-acids for repair of wastage is in proportion to their occurrence in the tissue proteins; their *tendency to dialyze* into the cells from the surrounding fluids is, on the other hand, in proportion to their relative concentrations in the fluids. In effect the cells have presented for their selection mixtures of amino-acids containing barely enough of some together with large surpluses of others. On certain diets, notably those in which the proteins are wholly of vegetable origin, much larger total quantities of protein have to be taken than would seem to be necessary, in order to provide enough of particular amino-acids which make up considerable percentages of human proteins, but only small percentages of vegetable proteins.

Fate of Amino-acids: Protein Storage.—The amino-acids appear to dialyze quite rapidly from the blood and tissue fluids into the

cells. The cells, in turn, utilize for the repair of wastage such quantities of the various amino-acids as they require. They also have a certain additional capacity for synthesizing their characteristic proteins, so that many kinds of cells, notably those of skeletal muscle, liver and spleen normally contain considerably more than just enough protein to maintain their protoplasmic organization. The surplus is built into the intrinsic cell structure and contributes its share toward the normal carrying on of cell function, yet can be dispensed with without injuring the cells irreparably. Thus in prolonged fever the muscles waste markedly and are correspondingly weakened, but are not otherwise harmed, and as their depletion is made good during convalescence they regain their former power.

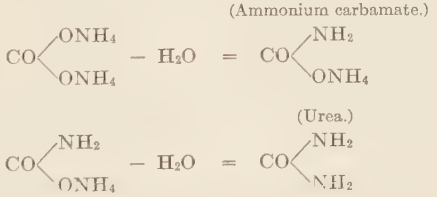
This surplus of cell protein above the minimum essential to protoplasmic organization appears to stand in the same relation to the circulating amino-acids as glycogen to circulating glucose (page 177). That is, it is added to up to the limit of the cells' capacity whenever amino-acids are present in surplus, or drawn upon whenever a deficiency of the same develops. Further consequences of this relationship are discussed below (page 184).

Fate of Amino-acids: Deaminization.—Whenever amino-acids are being actively absorbed from the alimentary tract "storage" proteins tend to be formed, as outlined above, with the result that there remain unutilized a mixture of such amino-acids as are in excess because they occur in larger proportion in the proteins taken as food than in those of the body, together with a further surplus due to over-ingestion of proteins beyond the capacity of the cells to store them. The excess would tend to charge the blood and tissues with amino-acids were it not for an interesting process known as *deaminization*, formerly believed to occur in all tissue cells, but recently shown (Bollman, Mann, and Magath) to be confined to the liver. The process consists of a splitting off of the amino (NH_2) radicals, forming ammonia, and leaving non-nitrogenous residues; the latter, after a further elimination of sulphur or phosphorus in the case of those amino-acids which contain one or the other, become radicals containing only carbon, hydrogen and oxygen. In other words, they come into the same general category with the chief non-nitrogenous foodstuffs, the carbohydrates and fats, and may be used similarly as fuel. Three of these residues, from valine, lysine, and tryptophane, appear to be oxidized promptly and directly; four others, from leucine, phenylalanine, histidine and tyrosine, undergo transformations yielding aceto-acetic acid (page 234); all the others, eleven or twelve in number, are converted into glycogen, and simply add themselves to the store of that substance in the body.

The relation of the liver to amino-acid metabolism may be summarized as follows: In the first place the liver cells have their own

basic metabolism, implying wastage and repair of proteins; for the latter process a definite amino-acid mixture is utilized. Secondly, the liver cells have considerable capacity to hold "storage" proteins. In the third place the liver cells have the property of deaminizing all amino-acids entering them except such as are utilized in one or the other of the above ways. The consequence of the last property is that the liver cells tend to keep their amino-acid concentration low. Hence whenever the concentration in the blood rises above the "dialysis threshold" (page 181) amino-acids dialyze from the blood into the liver to undergo deamination there. At or near the same threshold amino-acids begin to be eliminated also by the kidneys (page 436), a process wholly wasteful. The action of the liver thus conserves, for fuel purposes, amino-acids not immediately required in basic metabolism, the greater part of the surplus ingested above the quantities required to make good protein wastage and to fill the "protein storage" capacity of the tissues finding its way to the liver and being deaminized.

Urea Formation.—The ammonia produced in deamination combines promptly with carbonic acid, forming ammonium carbonate. This latter substance, in turn, is converted at once into *urea*, the process occurring exclusively in the liver according to the observations of the investigators cited above. The conversion is a dehydration, and is described as going on in two stages as indicated in the following equations:



Urea is eliminated by the kidney as fast as formed; hence the concentration in the blood is never high when conditions in the body are normal; the substance is, however, very slightly toxic, and quite high concentrations can be endured without demonstrable harm (page 236).

Deamination Leads to Excess Protein Consumption.—The tendency of the liver to dispose of all amino-acids in the blood above the "dialysis threshold" has an interesting and important consequence in relation to the uneven way in which we distribute our food intake during the day. Instead of taking small meals at equal and frequent intervals, so that the processes of digestion and absorption are practically continuous, we take the whole twenty-four hours' supply in three meals, more or less. The result is that after meals there are periods of abundant digestion and absorption,

followed by intervals in which little or none of either is going on (page 416). In the case of glucose the recurrence of periods of abundant absorption does not make much difference, because the glycogenic function of the liver usually takes care of all that is absorbed, and turns it back into the blood when needed, as glucose again. In the case of amino-acids there is a certain degree of storage as protein, but there is also practically always a large temporary surplus which is changed by deaminization into non-nitrogenous material, useful as fuel, but which cannot be turned back into protein. The consequence of this is that part of the protein we eat is diverted from its primary function as restorer of tissue waste to serve merely as fuel. If we were to change our habits so that we took a small meal every four hours throughout the twenty-four the absorption from the alimentary tract would be nearly steady, there would not be periodical "flooding" of the liver, not so much surplus amino-acid undergoing deaminization, and we would satisfy the protein requirements of the body with much less diversion of protein to a fuel use and so on a much smaller total consumption of proteins. The experiment has been tried on farm animals with the above result strikingly shown. This is not an argument in favor of changing our eating habits. Protein economy is only one of a number of factors that determine how food should be taken. Other factors, of more immediate importance, justify our present habits, in spite of the non-economy entailed (page 466).

Utilization of Stored Protein.—Whenever the wastage of protein by the cells outstrips the intake, as usually in the heightened basic metabolism of fever, or in starvation, the stored proteins are drawn upon to make good the loss. Probably all cells contain some protein in excess of their absolute requirements, but only the skeletal muscles, the liver and the spleen have stores which can be drawn upon extensively without injury to the cells. The mechanism for drawing upon these stores is apparently based on the equilibrium existing between the amino-acids of the blood and the proteins of the tissues (page 181). It is found that even in starving animals the concentration of blood amino-acids persists at about the normal level. But such vitally important cells as those of the heart and brain must have their repair requirements met or they will suffer damage. To meet these requirements, after such stored proteins as they themselves may contain have been used up, they draw upon the blood amino-acids, thereby tending to lower the concentration of the latter. Since the blood does not actually become less concentrated it is evident that the storage proteins must undergo reconversion into amino-acids, which latter must reënter the blood in amounts sufficient to make good all withdrawals.

The marked wasting of the skeletal muscles in fevers and in

starvation represents the sacrifice of storage proteins for the maintenance of essential tissues. There is evidence that stored proteins may serve also as sources of sugar to be used as fuel. In this case there is decomposition of the proteins into amino-acids followed by the deaminization of the acids, with production of non-nitrogenous fuel residues. In starvation this mechanism is brought into play, and also in phlorhizin poisoning and in diabetes (pages 179 and 180).

The Amino-acid Equilibrium.—The amino-acid requirements of individual cells are met by the constant presence of a definite amino-acid concentration in the surrounding blood and tissue fluid. The maintenance of this concentration depends on a complex equilibrium in which the chief factors are amino-acid intake by absorption from the digestive tract, synthesis of "storage" protein and its incorporation within muscle cells, liver cells and spleen cells chiefly, deaminization of surplus amino-acids in the liver and return of stored protein to the blood in the form of amino-acids in case of shortage.

Lipides in the Cell Environment.—In Chapter I (page 20) it is stated that phosphatides are important constituents of protoplasm. This fact leads us to expect to find phosphatides also present in the cell environment. We do not know whether there is a wastage of cell phosphatide in basic metabolism comparable to the wastage of cell protein. Inorganic phosphates are normally given off from the body in the urine, and it is conceivable that they may be derived, in part, at least, from disintegration of cell phosphatides. Such a wastage would imply the presence of phosphatides or phosphatide precursors for repair purposes. The fact is that both phosphatides and fats, the latter being essential constituents of phosphatides, are present in blood and tissue fluids. For convenience of discussion fats and such fat compounds as occur in the body are spoken of jointly as *lipides* (Bloor). Whether lipides serve as tissue-repair materials in a manner comparable to blood proteins or not it is known that they do supplement carbohydrates (glucose and glycogen) as fuel materials. We can thus account for their presence satisfactorily from the standpoint of their use as fuel whether or not they also have a repair function.

When no fat is being absorbed from the alimentary tract the concentration of lipides in blood is rather low (0.68 per cent total lipides in normal plasma, according to Bloor) and tends to be fairly constant. Whatever is taken up by the tissues for use in metabolism is replaced from the stored supplies in the *adipose* tissues. In these tissues the stored lipides are almost wholly in the form of uncombined fats. A considerable mass of evidence points to the conclusion that fats must be changed to carbohydrates (glucose or glycogen) in order for the tissues to be able to use them in metab-

olism. This change is chemically complex, involving preliminary "desaturation" of the fatty acid radicals and also formation of "ketone bodies" (page 234). It has been shown that the changes in the structure of the fat molecule which attend the conversion to carbohydrate are carried on largely in the liver.

The Control of Fat Metabolism.—According to the view of Macleod and associates the control of fat metabolism is to be pictured as follows: the adipose tissues have an innate tendency to discharge their fats into the blood to be conveyed to the liver where the conversion of fats to carbohydrates through a stage involving ketone body formation occurs. This tendency is inhibited more or less completely by the presence of insulin in the blood. The consequence is that whenever blood-sugar concentration is high enough to induce discharge of insulin from the islands of Langerhans little or no conversion of fats to carbohydrates takes place. Conversely, whenever blood-sugar falls below the concentration at which the islands are stimulated fats are discharged from the adipose tissues.

The immediate fate of fats absorbed from the alimentary tract after meals evidently depends on whether the blood contains much or little insulin. If insulin is present in abundance fats cannot be converted to carbohydrates, and since they disappear from the blood in six to ten hours must be deposited in the adipose tissues. Indeed this has been proved by experiment to happen. If insulin is deficient on the other hand, absorbed fats may be taken up by the liver and converted to carbohydrates.

The constant utilization of carbohydrates by the cells in metabolism tends to keep the blood-sugar near or below the threshold of insulin discharge, consequently conversion of the fats of the blood to carbohydrate may go on during much of the day. As a matter of fact about 30 per cent of all the energy released in metabolism is derived from food fats on an ordinary diet (page 467). Thus the metabolism of fats is not to be thought of as beginning where carbohydrate metabolism leaves off, but rather as complementary to it; both proceed side by side, the body obtaining its supply of energy from the different nutrients in proportion to their consumption in the food.

Lipemia.—In starvation, after the stored glycogen has been pretty well exhausted, the blood usually contains more than the normal concentration of lipides. The condition is called *lipemia*. The explanation is that in the shortage of glycogen the adipose tissues discharge their fats at a much higher rate than ordinarily. The increased concentration of blood lipides is due to the movement in the blood stream of these substances in quantity sufficient to provide substantially all the fuel the body is using instead of only a fraction of it as they do when carbohydrates are available in abundance. A similar lipemia is characteristic of diabetes mellitus, on

account of the failure of insulin (see above). In severe cases the total lipides of the blood plasma may be three times the normal (Bloor).

Lactating mammals are giving out considerable quantities of fat from their bodies daily in their milk. The consensus of opinion appears to be that milk fat is derived directly from blood phosphatides (Meigs). In such animals, therefore, enough phosphatides must be moving in the blood to provide the amounts required for milk-fat formation, as well as for the special phosphatide requirements of the body. Direct examination of the blood shows that there is usually a somewhat higher concentration of total lipides in the plasma of lactating than of non-lactating animals. In other words, a moderate lipemia is a feature of lactation.

One effect of poisoning an animal with phlorhizin or phosphorus is to cause a very active discharge of fats from the adipose tissues into the blood. This leads both to marked lipemia and to a very pronounced taking up of fat by the liver, so that the organ may contain more than half its weight of fat. This fact constitutes additional evidence favoring the view that the liver plays an intermediate role in the conversion of adipose tissue fat to utilizable fat derivatives.

Equilibrium Among the Nutrients. -It should be clear from the above paragraphs that the body is able to use as fuel not only the glucose obtained directly from the carbohydrates of food, but also glucose derived through a glycogen stage from the non-nitrogenous residues of surplus amino-acids. Fats also serve as fuel, but according to the weight of present opinion only after they have been converted into glucose (page 52). In an individual who is neither gaining nor losing weight, and whose total water content is uniform, the total daily utilization of nutrients in metabolism just balances the daily intake of the same in the food (allowance must be made, of course, for undigested material). A certain definite quantity of amino-acids goes to make good protein wastage; possibly some phosphatides serve a similar purpose in making good phosphatide wastage. The whole remaining amount of nutrient material is oxidized with liberation of energy. In man on an average mixed diet a little less than two-thirds of the total energy of the food is contained in the carbohydrate eaten; the remaining energy (slightly over one-third), is divided between protein and fat roughly in the ratio of 1 to 2 (page 467). This is an average distribution of the energy of the diet, but since among civilized human beings what is eaten usually depends largely on what happens to be served, and in savages on what can be got, it is clear that there must be very frequent wide departures from the average in individual cases. The equilibrium among the nutrients is such that wide variations in the intake of different nutrients have little or no immediate effect on metabolism,

provided the total quantity is adequate. The cell environment contains glucose, amino-acids and phosphatides. There are reservoirs of glycogen in the liver and muscles, proteins in the skeletal muscles, liver and spleen, fats in the adipose tissues. At intervals additional quantities of the different classes of nutrients enter the blood from the alimentary tract. The cells use fuel in accordance with their metabolic demands; these in the case of skeletal muscles may be twenty to thirty times as large in maximal activity as in rest. Thus the consumption of fuel varies from moment to moment. Whenever metabolism is vigorous and prolonged the glucose supply rapidly falls off. The islands of Langerhans become wholly inactive; glycogen is converted into glucose and discharged into the blood; and coincidently with this "mobilization of fat" begins. That is, either food fats as they enter the blood from the alimentary tract, or adipose tissue fats, begin to be converted actively into sugar, apparently through the liver as an intermediary (page 186). Any surplus amino-acids that are present are deaminized, and thus contribute their non-nitrogenous residues to help make good the glycogen supply. Through these interactions the various classes of nutrients all play their part in providing the body with the fuel it needs.

Storage of Nutrients.—Whenever the intake of nutrients exceeds their utilization by the body the surplus is deposited in the storage tissues. An interesting feature of this deposition is that it is not confined to the formation of glycogen from glucose, adipose tissue fat from blood fat and storage protein from amino-acids. It is true that excess glucose apparently tends first to be converted into glycogen, but as the glycogen content of the body as a whole becomes high in relation to the fat content a part of the surplus glucose begins to be changed into fat. If the excess of glucose persists after the tissues have accumulated all the glycogen they can hold the entire surplus changes into fat. This fact of itself shows that there is an equilibrium between glycogen and glucose on one hand and fats on the other leading under proper conditions to the production of fat from glucose. An additional fact supporting this indication is that in lactating animals on fat-free diets the milk contains fat, some or all of which is necessarily derived from the carbohydrates and deaminized protein residues of the food. In animals on such a diet, provided food is abundant enough, milk production may be maintained for a long time, and the animal may, at the same time become fatter. This can happen only because carbohydrates and deaminized proteins serve as sources of milk fat as well as of body fat.

Undoubtedly the reader has perceived by this time that difference of opinion exists over whether the body possesses the power to change fat into carbohydrate. A fact favoring the theory is that hiber-

nating animals enter their winter sleep very fat and come out of it lean, but with the liver heavily charged with glycogen. Studies of the respiratory exchange (page 459) show that oxygen is breathed in during hibernation which is not given out again in products of oxidation. The simplest way to account for this retention of oxygen in the body, indeed the only way at present, is to suppose that it is utilized in the conversion of fat molecules into carbohydrate molecules, the latter containing more oxygen proportionally than the former.

Summary.

Inorganic salts are essential constituents both of cells and cell environment. They occur in body fluids in much the same proportion as in sea water, although only about one-fourth as concentrated.

The distribution of salts between cells and tissues is such as to maintain osmotic and Donnan equilibrium. The concentrations of individual salts are not identical, however, in cells and fluids.

The intake of *sodium chloride* depends primarily on its use as a condiment, and ordinarily exceeds strict physiological need. The outgo balances the intake in the long run, although there is a lag in adjustment when marked variations in intake occur.

The *calcium* intake varies with the diet, averaging about 0.7 gm. daily in adults. Elimination balances intake except in children, in whom calcium deposition occurs continuously at the average rate of about 0.2 to 0.4 gm. daily.

Lactating animals contribute lime salts to their milk; when the diet proves inadequate as a source of supply the bones are drawn upon. The calcium content of the blood remains nearly uniform. The general equilibrium between blood calcium, bone calcium and food calcium is regulated by the hormone of the parathyroid gland.

On account of the high potash content of common vegetables the intake of *potassium* is usually higher than of any other inorganic salt except sodium. Outgo balances intake, presumably regulated by positive excretion by kidney cells.

Iron is an essential constituent of hemoglobin. It is excreted in small amounts, hence must be included in the diet.

Iodine is a constituent of the thyroid hormone, and so must be available in the diet. Sea water contains a trace of iodine, and wind-blown spray distributes iodine over considerable areas. Regions too remote from the ocean to benefit thus often reveal iodine deficiencies in both plants and animals.

The classes of *nutrients* are carbohydrates, proteins and fats. These are reduced by digestion to glucose (with levulose and galactose in small amounts), amino-acids and fatty acids and glycerol. The latter are resynthesized into fats during absorption.

During periods of active absorption from the digestive tract the

concentrations of glucose, amino-acids and fats in the blood tend to rise. At other times, on account of the utilization of nutrients by the tissues, the concentrations tend to fall.

Glucose occurs normally in the blood and tissue fluids in concentration of 0.10 to 0.12 per cent. Its presence in the blood in excess of the upper limit constitutes *glycemia*. Sugar in urine constitutes *glycosuria*. The condition follows the introduction into blood of any amount whatever of disaccharides. It will not be caused by *glucose* in a healthy individual except as the result of glycemia amounting to 0.17 per cent; the latter representing the reabsorption limit of the kidney for sugar.

Glucose tolerance is the measure of the ability of the body to utilize and store carbohydrate hour by hour. So long as the input of glucose does not exceed the tolerance no glycosuria occurs. As the limit of tolerance is passed a portion of the surplus sugar appears in the urine. There is a second limit above which all excess sugar is given out in the urine.

Carbohydrate is stored in liver and muscles in the form of *glycogen*. The hydrolysis of glycogen to glucose is catalyzed by the enzyme *glycogenase*. The reverse synthesis of glucose to glycogen has not yet been shown to be catalyzed by an enzyme. The glucose-glycogen equilibrium is so adjusted that when the blood-sugar concentration exceeds about 0.12 per cent glucose converts to glycogen; when the concentration falls below this figure glycogen converts to glucose.

According to present conceptions the conversion of glycogen to glucose is inhibited by insulin in the blood. The stimulus to insulin out-pouring from the islands of Langerhans is thought to be blood-sugar concentration above 0.12 per cent.

"Mobilization of sugar" may be caused by irritation of a particular spot in the medulla (piqûre) or by stimulation of the great splanchnic nerves. In both cases the effect may be attributed to nervous excitation acting directly on the liver cells. Splanchnic stimulation may also act indirectly through causing the discharge of adrenin from the adrenal bodies. This hormone appears to have the property of exciting the liver cells to discharge sugar into the blood. The mobilization of sugar by adrenin is looked upon as one phase of the "emergency mechanism" of the body.

Phlorhizin induces glycosuria in part by suspending the power of the kidney cells to reabsorb sugar. All that filters through the capsular membranes appears in the urine.

The tolerance of the body for glucose is in direct proportion with the amount of *insulin* present. This is because the ability of the tissues to take up sugar, either for utilization or storage, depends on the presence of the hormone. When insulin is deficient glucose accumulates in the blood. This glycemia tends ordinarily to gly-

cosuria. When insulin is unduly abundant the tissues take up sugar at an excessive rate. The concentration of blood sugar consequently falls. Definite symptoms, including convulsions and coma, and culminating in death, attend marked decreases in blood sugar due to excess insulin.

Digestion and absorption of the proteins of the food result in the introduction into the blood and tissue fluids of mixtures of *amino-acids*. The cells utilize the various amino-acids primarily for the repair of protein wastage and secondarily for the synthesis of "storage" protein, for which perhaps all cells, certainly those of liver, spleen and skeletal muscle, have considerable capacity.

Surplus amino-acids undergo *deaminization* in the liver, whereby non-nitrogenous residues are formed. These may be converted into glycogen or possibly in the case of two or three used directly for fuel. The nitrogenous radicals, split off in the process, form ammonia, which is converted into urea and eliminated by the kidney.

Amino-acids enter the liver and are deaminized whenever their blood concentration exceeds the "dialysis threshold" of 5 mg. total acids per 100 gm. blood. During periods of active absorption from the alimentary tract this threshold is exceeded with the result that after meals there is active deaminization. Furthermore the deaminization is greater after meals abundant in protein than after meals poor in protein; it also follows that the custom of taking the total day's supply of food in three meals, more or less, is uneconomical in respect to protein, since it entails considerable diversion of protein from its primary function as restorer of tissue wastage to a secondary use as fuel.

Utilization of stored protein occurs whenever the wastage of proteins from the cells exceeds the intake. The chief stores of protein are in the cells of the liver, spleen and skeletal muscles. These same stores may also be drawn upon to serve as fuel in times of general fuel shortage in the body.

The amino-acid equilibrium of the body involves the following factors: Amino-acid intake from the digestive tract; synthesis of "storage" protein and its incorporation in the cells; deaminization of surplus amino-acids; return of stored protein to the blood in time of shortage. These factors interact to provide the cells of the body at all times with the amino-acids they require for carrying on their basic metabolism.

Lipides (fats and phosphatides) may possibly serve a repair function in making good wastage of phosphatides from the cells. They are known to supplement glucose and glycogen as fuel material. The lipide concentration of the plasma when no fat is being absorbed tends to be low and fairly constant.

Fats are thought to be converted to carbohydrates before being oxidized by the tissues. The synthesis of carbohydrate from fat

involves a preliminary "desaturation" of fat molecules and a formation of "ketone bodies," both taking place wholly in the liver. One function of insulin appears to be to inhibit this process.

Lipemia is a condition in which the lipide concentration of the blood is higher than normal. It is commonly seen in starvation and in diabetes when the fat reserves are being called upon to satisfy the major fuel requirements of the body. Lactating mammals show moderate lipemia on account of the large movement of phosphatides in the blood in connection with the production of milk fat. Poisoning with phlorhizin or phosphorus causes the adipose tissues to discharge large quantities of fat in a short time, thus producing pronounced lipemia. A feature of this action is that the liver becomes heavily charged with fat. The presumption is that all the fat that leaves the adipose tissues is taken up by the liver as a preparatory stage of carbohydrate synthesis.

There is an equilibrium among all the nutrients of such a character that the concentrations in the blood of glucose, amino-acids and phosphatides tend to be fairly constant. At the same time the varying fuel demands of the body are fully met. These conditions are maintained in spite of variations from moment to moment in total metabolism, and of fluctuations from day to day in the absolute amounts and relative proportions of the various nutrients ingested. The storage tissues function as reservoirs in this equilibrium, giving off or taking up materials according as utilization or ingestion is in the ascendence.

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CHAPTER XII.

CELL ENVIRONMENT: VITAMINS AND HORMONES.

VITAMINS.

That vitamins are essential factors in metabolism has already been pointed out (page 55). These substances, with one exception (see below), are synthesized only by plants and are taken into the bodies of animals in their food. The digestive processes appear not to alter any of the vitamins in any essential way. So far as known, they pass from the alimentary tract into the blood in substantially the form in which swallowed. They circulate in the blood until taken up by the tissue cells. Very little is known as to the quantities of vitamins in food, the rate of their uptake by the cells, or their ultimate fate. Detailed knowledge of these points awaits the isolation of vitamins in pure state. Thus far three apparently pure substances showing the properties of vitamins (vitamins A and B and bios) have been obtained (pages 194 and 197), but experiments with them have not yet been carried far enough to give detailed information about their action.

Chemical study of as pure preparations of the various vitamins as have been obtained indicate clearly that they fall into two distinct chemical classes. One class is nitrogenous, and its members all have presumably the chemical organization characteristic of the *amines*. The other is non-nitrogenous and consists, so far as can be judged at present, of substances belonging to the *sterol* group.

Our early knowledge of vitamins was obtained by studying the effects on metabolism of long periods of nourishment on food mixtures in which all factors were kept adequate except one, that one being the particular vitamin under investigation, which was either absent or much reduced in quantity. This kind of study showed the existence of various distinct vitamins, and made possible quite definite statements as to their characteristic physiological properties. It did not, however, offer any satisfactory basis on which to assign names to them. The practice accordingly arose of designating them by letters of the alphabet. The generic name "vitamin" is a contraction of the word vitamine, proposed by Funk shortly after his first studies (1911), indicated at least one of the substances of the class to be chemically an *amine*. When several substances belonging to the group were shown to be non-nitrogenous the name vitamin was adopted, to preserve a designation grown familiar

through usage without implying any specific chemical constitution. The following individual vitamins are now recognized: A, B, C, D, and E. A vitamin-like substance, *bios*, is also to be included. A, D and E are sterols; B, C and bios amines.

Vitamin A.—A non-nitrogenous extract (sterol) thought to be nearly pure vitamin A has been isolated from cod-liver oil, butter, egg-yolk and other sources. The vitamin has been had in impure state from these same sources for several years. Though obtained most easily from animal sources in the laboratory, the vitamin appears to be synthesized only by plant tissues and to be taken by animals in their food. The evidence indicates that many plants contain vitamin A. Actively growing parts contain much higher concentrations than do storage structures. Hence leaves and stems are richer than are the endosperm portions of seeds or fleshy roots. Animals store considerable amounts of vitamin A in their bodies beyond their immediate requirements (chiefly in liver, kidney and adipose tissues; little or none in muscles), provided their diet has provided a surplus. The vitamin is spoken of as "fat soluble," because its occurrence in animal tissues is in solution in fats. In plant tissues it appears that the vitamin is not in association with fats, at least not ordinarily. Milk and egg-yolk contain particularly high concentrations of A, representing accumulation of the material for utilization by growing young. Fish-liver oil (cod-liver oil) is very rich in A. This is more probably because the food of fish contains it abundantly than because fish have particularly great metabolic need for it.

Vitamin A must be present in the body of a mammal if it is to maintain good nutritive condition. Complete deprivation leads to a decline, culminating in death; this is especially striking in young animals. Entire recovery follows administration of minute amounts of the pure substance mentioned above, or larger amounts of A-containing food-stuffs. A feature of the decline is marked susceptibility to infection. An eye disease (xerophthalmia), usually develops in experimental animals deprived of A, and evidence is accumulating that the susceptibility of human beings to many infections is greater when A is deficient in the body than when it is abundant.

Particularly striking is the failure of young animals to grow on diets otherwise adequate, but lacking in vitamin A. This relationship has caused A to be spoken of as the "growth-promoting" vitamin. At the present time it is not known whether A has a specific influence on growth metabolism (page 63), or whether failure of growth is a secondary effect of the general decline which results from deficiency of A.

Vitamin B.—At least three very different properties are attributed to this "water-soluble" vitamin. These are: (*a*) The prevention of the type of neuritis known as beriberi; (*b*) the promotion of

growth; (*c*) stimulation of the appetite (only in the first of these properties does B appear to be unique). In 1925 Bowman and Yeo reported that they had isolated from a Chinese bean, Phæolus aureus, a crystalline product with a definite melting-point, which they assume to be pure vitamin B. This substance in minute quantity alleviated severe symptoms of neuritis in pigeons in which the neuritis had been induced by feeding a diet deficient in B. It also stimulated the appetite of the pigeons so that following each administration they ate increased quantities of the polished rice (B-deficient) on which they were fed. Prior to this isolation of what appears to be the pure vitamin various highly concentrated preparations had been made. A water-soluble extract of milk (not identical with fat-soluble A which milk also contains), was found to promote growth in young rats. The active agent in this extract is the substance to which the designation B was first assigned (by McCollum). An extract, assumed also to contain B, had been prepared from various plants several years before the pure product was isolated. This plant extract showed properties identical with those described above for pure vitamin B.

The most abundant plant source of vitamin B is yeast. It occurs also in the embryos and hulls of grain, but is nearly or quite wanting in the endosperm. Thus polished rice, which includes only endosperm material, is devoid of B, while the polishings are rich in it. The green parts of most plants contain considerable concentrations. This was one of the first of the vitamins to be studied by modern methods; it is the one which was first shown to be probably an amine (Funk), leading to the proposal of the name vitamine.

Although eggs and milk are rich in vitamin B it is not known to occur in high concentration in any body tissues. In other words, there is little storage of B in the animal body. The quantities found in eggs and milk are apparently passed there quite directly from the diet of the egg-laying or lactating organisms.

Vitamin C. From time immemorial long sea voyages, such as those of whaling ships, have been attended by outbreaks of scurvy. These have been rightly attributed to deficiencies in the diet, which on such voyages usually became reduced to salt meat and ship biscuit, soon after which outbreaks of scurvy were to be looked for. It has also been known for a long time that scurvy is prevented, or after onset cured, by eating fresh fruits or vegetables. These facts, generally known, particularly among sailors, have been brought into line with our broad conception of vitamin action by the discovery that a water-soluble extract of certain foods prevents or cures scurvy, while its lack leads to the development of the disease. This antiscorbutic vitamin, designated as *vitamin C*, is present abundantly in such juicy fruits as oranges, lemons and tomatoes.

Leaves, growing shoots, immature vegetables, and sprouting grains are also rich in C. The less juicy fruits and vegetables, like apples, bananas and potatoes, contain somewhat less but still considerable amounts. Root vegetables and mature seeds are nearly devoid of the vitamin.

The occurrence of C in the bodies of animals or in their milk depends on the C value of their food. Cattle on pasturage give milk much richer in C than do cattle on a dry winter ration. Similarly the flesh and blood of animals are richer in the vitamin when they have had a diet rich in C than when it has been poor. Vitamin C, as already stated, is an amine.

Vitamin D.—The first indication of the existence of vitamin D arose from the discovery that cod-liver oil is both a preventive and a cure of rickets in children and experimental animals. Rickets (rachitis) is a condition of disturbed metabolism whose most conspicuous feature is the failure of normal deposition of lime salts in the bones. Both lime and phosphoric acid are necessary to this deposition. It follows that the diet must include certain quantities of both if rickets is to be avoided. It was shown, however, that rickets may develop even with both calcium and phosphoric acid present in the blood in adequate amounts. When this happens administration of cod-liver oil promptly brings about a cure. At first this beneficial action was attributed to vitamin A, in which cod-liver oil is known to be rich. But butter, which also contains a high concentration of A, does not benefit the rachitic organism as cod-liver oil does. Furthermore, the vitamin A in the oil can be destroyed, as by aërating vigorously at 100° C., without impairing the antirachitic property. This evidence leads to the conclusion that a separate vitamin is concerned, for which McCollum proposes the designation vitamin D.

Since 1890 evidence has been accumulating that ultra-violet radiation falling on the bodies of children or experimental animals prevents rickets, or cures it if already present. Since the discovery of vitamin D it has been shown that the two agencies are interchangeable. Children with rickets may be cured either by direct exposure to ultra-violet light (sunlight is adequate provided no glass intervenes to cut off the short wave lengths), or by administration of cod-liver oil. The above statement assumes, of course, that the diet includes adequate amounts of lime and of phosphoric acid. An explanation of this interchangeable action was afforded by the announcement in 1924 (Steenbock and Hess), of the discovery that various inactive fats, *i. e.*, fats showing no antirachitic property, develop the property when irradiated with ultra-violet light. It appears that fats circulating in the cutaneous bloodvessels may thus acquire antirachitic action when the skin is exposed to suitable radiation. Cholesterol takes on the property when similarly irra-

diated, a fact which strengthens the view that this and other non-nitrogenous vitamins are sterols.

Vitamin E.—In 1922 Evans and Bishop showed that certain diets, adequate in all respects for the growth and maintenance of individual rats, are inadequate for reproduction. In other words, rats thrive on these diets, but are sterile. Fertility is restored by adding small quantities of lettuce, wheat germ, dried alfalfa, meat, rolled oats, or large quantities of milk fat. There is a substance, presumably a vitamin, present in these latter foods, but absent from such foods as casein, lard and cornstarch, on which rats are frequently fed in growth experiments. Other investigators (Sure) showed the vitamin to be fat-soluble, and to be present particularly in vegetable oils, such as of yellow corn, wheat germ and hemp seed. Thus the vitamin falls in the class of sterols.

The process of reproduction includes many factors, and sterility may therefore have various causes. One effect of E deficiency pointed out by Evans and Bishop is resorption of the embryos by the mother after gestation is well under way and proceeding apparently normally. Effects of lack of E can also be demonstrated, however, in abnormalities of the germinal tissues themselves. The action of the vitamin thus appears to be complex.

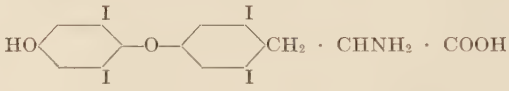
Bios.—In 1901 Wildiers showed that an extract of yeast prepared by him promotes markedly the growth of yeast cells. This extract is soluble in water and alcohol; insoluble in ether. Wildiers proposed the name *bios* for his substance. Since 1918 several workers have confirmed the original finding. By some bios has been identified with vitamin B, in which yeast is particularly rich. The weight of evidence at present indicates, however, that they are separate substances. In 1924 a crystalline material with a sharp melting-point was isolated from yeast, and found to promote the growth of yeast cells (Eddy, Kerr and Williams). This appears to be pure bios. It has been shown to be a nitrogen compound. In relation to plant cell metabolism bios undoubtedly acts as a vitamin. Whether it has any vitamin action on the animal body is not yet clear. Investigations that have been made possible by the isolation of the pure substance should determine this and many other points.

HORMONES.

These substances are synthesized within the animal body out of raw materials present in the blood and tissue fluids. In the main they are the products of endocrine glands (page 149). Hormones were originally conceived as chemical *excitants;* the name "hormone" expresses this idea. Continued study has shown, however, that these agents influence metabolism in a variety of ways, so that

while the name "hormone" remains in common use its strict connotation no longer holds. On account of the diversity of action of the different hormones and in the interests of brevity no attempt will be made here at general statements applicable to all hormones. Certain of them are so specialized in action that they can best be considered in connection with particular bodily processes. Secretin, for example, is discussed in connection with its function as an excitant of digestive secretions (page 411). Hormones of this type will not be treated in this section. Brief summaries will be presented covering present knowledge of those that exert a more general influence. Reference is made at the end of the chapter to works giving fuller details.

Thyroxin.—This compound is synthesized in the cells of the thyroid gland and discharged thence into the blood stream. It has been shown by Harington to have the empirical formula $C_{15}H_{11}O_4NI_4$ and to be β – [4 – (4′ – hydroxyphenoxy)phenyl] – α – amino-propionic acid, in which four iodine atoms have been substituted for four hydrogens. According to Harington, the probable position of the iodine atoms is as indicated in the accompanying structural formula:



In the view of Kendall, thyroxin acts as a hydrogen transporter (page 50). There is direct evidence that increasing the amount of thyroxin in the body increases the basic metabolism. Also that decreasing the amount lessens basic metabolism (page 462).

Evidence has been advanced to show that in the bodies of mammals, including man, given quantities of thyroxin will accept definite amounts of hydrogen (Boothby and Sandiford). In other words, the effect of thyroxin on metabolism appears to be quantitative. Expressing the effect in terms of the heat produced by the physiological oxidations which the thyroxin promotes, it is stated that 1 mg. of thyroxin leads to the production of approximately 1008 Calories of heat. The increased metabolism resulting from the administration of thyroxin comes on gradually, reaching its peak in man in about eight days, and persisting for twenty days or more. This fact shows that each molecule of thyroxin must function as a hydrogen transporter a great many times before it loses the property. There is a small continuous loss or destruction of thyroxin in the body, estimated to amount to about 0.2 to 0.4 mg. daily. The total amount present at one time in the normal individual is calculated to be about 12 to 14 mg. The presence in the cell environment of more than normal amounts of thyroxin con-

stitutes the condition of *hyperthyroidism*. Less than normal amounts give *hypothyroidism*.

Hyperthyroidism.—Transient hyperthyroidism may be induced by administering to a normal animal or man either thyroxin or a thyroid extract containing a high concentration of the same. Administration may be by mouth, as the digestive juices do not destroy the hormone. Chronic hyperthyroidism involves over-activity of the thyroid gland. Not much is known as to the conditions which bring about such over-activity. There is some evidence that the gland is subject to nervous influences, and that its over-activity may be due to over-excitation (Cannon and associates). Whatever may be the cause the fact remains that some human beings develop hyperthyroidism as a chronic condition. The symptoms are, in general, such as would be expected to attend a general heightening of the basic metabolism. They include a tendency to emaciation associated with a hearty and even voracious appetite, and usually an abnormally great food consumption. The heart beats rapidly and forcibly, often irregularly; the peripheral bloodvessels are dilated. The nervous system is hyperexcitable. This condition manifests itself often by marked irritability; sometimes there is insomnia; occasionally a tendency to hallucinations; the intelligence seems not to be affected. The prominent eyes, which are memorialized in the name of one type of the disease, "exophthalmic goiter," are said to be due to a crowding forward of the eye-balls by chronic spasms of smooth muscles behind them in their sockets.

Aberrant Thyroid Function.—True hyperthyroidism implies the production of more thyroxin than normal, and hence the utilization of more than normal quantities of iodine. There is a disease, similar in the main to hyperthyroidism, in which it is doubtful whether excess quantities of iodine are being utilized; in fact less than normal quantities may be available in the diet. A suggested explanation (Plummer) is that the functional metabolism of the gland undergoes a change such that instead of 4 atoms of iodine being incorporated in each thyroxin molecule only 1 or 2 are incorporated. The modified thyroxin thus formed is assumed to be a more active hydrogen transporter than ordinary thyroxin, and perhaps to have specific injurious effects besides. Certain characteristic differences between true hyperthyroidism (toxic thyroid adenomata), and exophthalmic goiter (diffuse hyperplasia), are thus accounted for. A fact reinforcing this view, and incidentally of great clinical significance as well, is that beneficial effects are obtained in disorders of the second type by dosage with iodine. One can scarcely imagine how such treatment could be of value in true hyperthyroidism, whereas if the gland were failing to incorporate enough iodine per molecule in its hormone it might be caused to

do so through the mass action of relatively large quantities of iodine in its cell environment.

Hypothyroidism.—Children are occasionally born without functional thyroids, or suffer atrophy of the glands in early life. Adults may also show degeneration of the same. Operative removal of all or part of the gland has also been found necessary in some instances. The effect of any of these is to deprive the individual of his normal supply of thyroxin, in whole or in part. It may also happen, as already pointed out (page 175), that there may be insufficient iodine in the diet, so that persons with otherwise normal thyroid glands may be unable to synthesize enough thyroxin for the needs of the body. Whatever may be the cause of the hypothyroidism, the effects on the body are attributable to the general lowering of the level of basic metabolism. They are, on the whole, opposite to those which attend hyperthyroidism. For example, the tendency is toward obesity, even though the appetite may be diminished. The heart is slow and the beats weak; the peripheral bloodvessels are contracted. There is a general sluggishness of the nervous system, attended with lowering of intelligence. In severe cases this amounts to complete idiocy.

Cretinism, Myxedema and Endemic Goiter.—Individuals who have never had functioning thyroids, or who have suffered atrophy of the glands in infancy, are called *cretins*. Their condition is described as *cretinism*. The situation that develops following degeneration or operative removal of the gland in adults is known as *myxedema*. Both these types of hypothyroidism may be benefited, or in case no other essential organs are involved completely cured, by administration of thyroxin or thyroid extract by mouth. To maintain the normal state administration must be continued throughout life. In regions deficient in iodine a considerable percentage of the population shows enlargement of the thyroid; the condition is called *endemic goiter*. This is looked upon as a compensatory reaction, tending to make good the thyroxin deficiency by heightened activity on the part of the gland. As a matter of fact the compensation is not successful, nor can it well be in the presence of an iodine shortage. Sufferers from endemic goiter accordingly show more or less indication of hypothyroidism. Marked benefit is derived in these cases by inclusion of iodides in small amount in the diet (page 175).

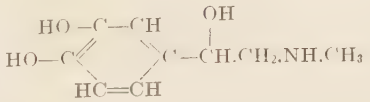
Parathyrin.—In 1924 Collip obtained from parathyroid glands an extract containing their hormone in high concentration. Schafer had previously proposed the name *parathyrin* to be applied to this hormone when isolated. The action of the hormone on the body has not yet been fully worked out. Collip has shown that it is directly related to the calcium metabolism (page 174), in that increases in the amount of the hormone, as by injecting a dose into the vessels of an animal, are followed regularly by increases in blood

calcium. It appears that lessening the amount, by removal of some or all of the parathyroid tissue, gives rise to calcium deficiency, although an actual lowering of blood calcium has not always been seen.

Certain characteristic bodily disturbances follow degeneration or operative removal of the parathyroids. These are believed by a number of investigators to be secondary results of the disturbed calcium metabolism, although it remains to be definitely proved whether they are of this nature or not. The bodily disturbances are grouped under the designation "parathyroid tetany." They range, according to the extent of the hormone deficiency, from spasmodic contractions of a few muscles to severe convulsive seizures, culminating in death from cramp of the respiratory muscles. There is evidence that the acute attacks are brought on through the agency of materials of protein origin absorbed from the alimentary tract. These materials are more abundant when the diet contains meat. It follows that carnivorous animals as a class, and human beings on a meat diet, are particularly subject to tetany when suffering from parathyroid deficiency. Experimental animals from which all parathyroid tissue has been removed are protected completely from tetany, no matter how much meat they may eat, by injection of a small dose of Collip's active parathyroid principle every twenty hours.

Injection of the hormone in such quantities as to raise its concentration in the blood above normal brings about undue concentration of calcium in the blood. The condition is designated *hypercalcemia*. The latter may be carried to such a point by excessive injection of the hormone as to cause nausea and vomiting, coma and death.

Adrenin (Epinephrine). —This hormone is synthesized in the so-called *chromaffin tissues*, which include the medullary portions of the *adrenal* bodies (also frequently called *suprarenal* bodies), and cells similar in staining reaction to those of the adrenal medulla, found in sympathetic ganglia and along the abdominal aorta. Adrenin was the first hormone to be obtained in pure state and so to be identified chemically. Its molecule is complex, as indicated by the structural formula:



The hormone has very characteristic effects on certain bodily tissues; these effects are described in more detail below. Some of them are produced by it in extreme dilution. Thus 1 part of adrenin in 400,000,000 to 800,000,000 of solvent is stated to cause a perceptible reaction on strips of rabbit intestine (page 418). This

great delicacy makes possible the assaying of fluids containing very little adrenin. Repeated assays have been made of the adrenin content of the venous blood as it leaves the adrenals, and from these assays the adrenin concentration of arterial blood has been calculated. The results indicate that under average bodily conditions this concentration is of the order 1 to 500,000,000 to 1 to 1,000,000,000. (It appears that adrenin dialyzes out from the blood during the passage through the capillaries, so the only *venous* blood to contain the hormone is that in the veins between the adrenals and the heart.)

Nervous Control of Adrenal Secretion.—The minute quantity of adrenin typically present in arterial blood represents a continuous slight secretion from the adrenal medulla. (It appears that the accessory chromaffin tissues contribute little or none.) If all the nerves supplying one adrenal body are severed the output of adrenin from that body at once drops to nothing, or at least to so low a value as to be non-demonstrable. This indicates that the ordinary secretion is the result of nervous excitation. Furthermore, artificial stimulation of the splanchnic nerves brings about a greatly increased output of adrenin. We have thus in the adrenal medulla a clear case of an endocrine gland whose output is regulated nervously. An *efferent* nervous pathway to an organ ordinarily implies *afferent* paths by which the organ may be excited reflexly. In the case of the adrenals evidence in support of the existence of such reflex paths has been advanced by Cannon and others.

The Function of Adrenin.—This hormone exerts definite influence on various bodily processes. The influence in most cases requires higher concentrations than are normally found in arterial blood, so that effects are seen only when the quantity is augmented, either by intravenous injection of adrenin, or by exciting the adrenal medulla to a greater discharge than normal. The predominant action is a direct stimulation of all tissues that receive innervation through the thoracico-lumbar (sympathetic) subdivision of the autonomic system (page 129). The sign of the action is the same as in stimulation through the sympathetic nerves. That is, adrenin excites or inhibits according as sympathetic stimulation excites or inhibits. One marked effect of sympathetic stimulation is vaso-constriction (page 334), with consequent rise of arterial pressure. Adrenin has this same action very markedly. Indeed this was the first influence discovered for it. For a time it was known as the blood-pressure-raising hormone. Some other effects due to its action on sympathetic terminations are dilatation of the pupils, quickening of the heart (this shows well only after the vagus nerves are cut, because adrenin also excites the cardio-inhibitory center; probably by an asphyxial effect, due to cutting off its blood supply by vaso-constriction; page 303), inhibition of the smooth muscula-

ture of the respiratory passages causing relaxation (an effect leading to its use in asthma), and inhibition of the smooth musculature of the alimentary tract (this is the most delicate of the adrenin actions). Adrenin also causes mobilization of sugar from liver glycogen (page 179), hastens the clotting of blood (page 273) and counteracts the fatigue of myoneural junctions (page 691).

The aggregate effect of the known action of adrenin is in one main direction, namely, to favor those bodily processes on which self-preservation depends in time of stress. This fact leads many physiologists to look with favor on the idea, developed by Cannon, that adrenin is, in essence, an *emergency* hormone, functioning relatively little in ordinary bodily conditions, but playing an active and important part in rallying the energies of the organism to cope with conditions of stress. Cannon and Britton have recently shown that muscular exertion is invariably attended by out-pouring of adrenin. This is clearly significant as an aid to vigorous effort in time of emergency. It is perhaps also an important factor in postponing fatigue in the routine use of the muscles. (For the relation of adrenin to temperature regulation, see page 448).

Insulin.—Since the work of v. Mering and Minkowski (1889) it has been clear that the utilization of sugar depends on the presence of a hormone elaborated in the *islands of Langerhans*, cell masses of characteristic appearance imbedded within the pancreas. Efforts to obtain an extract of island tissue displaying the properties of the hormone were only moderately successful until Banting (1922) proceeded on the assumption that the proteolytic enzyme present in extracts of whole pancreas destroys the hormone. By ligating the pancreatic duct the enzyme-secreting cells were caused to degenerate, leaving the island tissue fairly free. An extract of a gland so prepared was found to bring about active uptake of sugar when injected into the blood of an animal from which the pancreas had been removed, and thus deprived of the hormone. Subsequently, and fortunately for the practical development of insulin therapy, the discovery was made that alcohol extracts of fresh whole pancreas contain the hormone in potent form. Insulin, as used clinically, is an extract of whole pancreas, made primarily with acid alcohol and subjected to a series of purification processes. Attempts to establish its chemical identity are in progress at the present time. One group of workers (Abel and others) have announced the finding that the hormone property resides in a fraction characterized by a high percentage of "labile" sulphur (*i. e.*, sulphur whose linkage relationships are altered by boiling with $\frac{N}{10}$ Na_2CO_3), and furthermore that the potency of action appears to be directly proportional to the content of labile sulphur.

The functions of insulin as pictured by Macleod and associates are discussed earlier (Chap. XI). They may be summarized as

follows: (*a*) to reduce the glucose tension of the tissues, causing them to remove sugar actively from the blood; (*b*) to inhibit the action of glycogenase, and hence the conversion of liver glycogen to sugar; (*c*) to inhibit the tendency of fats to be converted to carbohydrates.

According to Sevringhaus and Smith the adequate stimulus to the island cells, causing them to discharge insulin into the blood, is the attainment of a blood-sugar concentration exceeding about 0.12 per cent (page 178). We have no information as to the normal con-

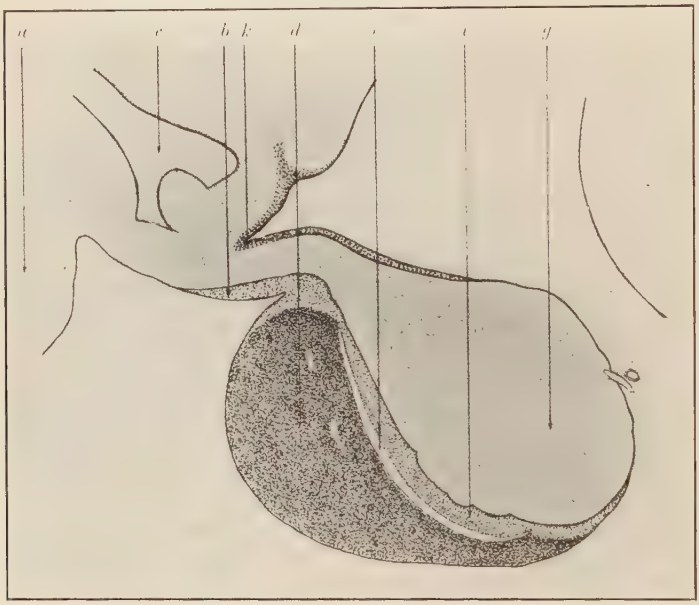


FIG. 22.—Mesial sagittal section of pituitary of adult monkey. *a*, optic chiasm; *b*, tongue-like process of pars intermedia (pars tuberalis of later writers); *c*, third ventricle; *d*, anterior lobe proper; *e*, epithelial cleft; *g*, nervous substance of posterior lobe; *i*, epithelial investment of posterior lobe; *k*, epithelium of pars intermedia (pars tuberalis), extending over and into adjacent brain substance. (Herring.)

centration of the hormone in the blood. It is used up or eliminated rather rapidly, as shown by the fact that the tissues begin to show loss of power to take up sugar quite soon (within a few hours) after removal of the last portions of island tissue. Furthermore, in severe cases of human diabetes administration of insulin twice daily is necessary. The administration must be intravenous or subcutaneous since the digestive enzymes render the hormone inactive.

Postpituitary Hormone.—The posterior lobe of the pituitary body (hypophysis) includes the *pars nervosa*, derived as an outgrowth from the floor of the third ventricle of the brain, and the *pars intermedia*, which arises as a subdivision of the pouch of buccal epithelium from which the anterior lobe is also derived (Fig. 22).

Some reason exists for considering the pars intermedia the true secreting gland, and the pars nervosa a storage organ from which the hormone is actually discharged. A small amount of tissue similar to pars intermedia tissue exists in the floor of the third ventricle and in the infundibulum. This is looked on as possibly accessory secreting tissue.

The stalk of the pituitary body connects the posterior lobe directly with the brain in the immediate neighborhood of the third ventricle, and considerable evidence exists indicating the possibility that the hormone of the posterior lobe may be discharged through the stalk and intervening brain substance into the cerebrospinal fluid, whence it passes into the blood (page 359). Not all investigators are agreed on this path of discharge; some incline rather to the opinion that the hormone passes directly into the blood stream as do the secretions of other endocrine glands.

Several apparently distinct bodily effects are seen following injection of extracts of posterior lobe. This fact has led to the view that the lobe produces several hormones. Abel and his co-workers have produced, however, a highly purified *postpituitary tartrate*, which shows the characteristic effects of ordinary posterior lobe extracts, although many times as potent as the best of them. The simplest conclusion is that the postpituitary produces only one hormone, although Draper has objected to this conclusion on the ground that in the tartrate the different effects are not augmented equally. The question must remain open until the hormone or hormones are obtained in indubitably pure state.

The important changes following injection of postpituitary extract are as follows: (1) A sharp and sustained rise of arterial blood-pressure (not seen in some species of birds nor apparently in reptiles, and not obtainable on repetition of the injection in any organisms yet studied; (2) a change in the volume of urine formed per unit of time (diuretic-antidiuretic action); (3) active contractions of the uterus, intestines and bladder; (4) augmented outpouring of milk from functioning mammary glands (galactogogue action); (5) in amphibia marked alteration of the pigmentation of the skin (melanaphore-expanding action); (6) active "mobilization" of sugar from the glycogen of the liver. Nos. 1, 3 and 5 appear to be special manifestations of a single property, that of exciting active contractions in smooth muscle or related contractile cells. Active contraction of the uterus (oxytoxic action) is the basis for physiological assay of the potency of any given postpituitary extract. The pronounced effects small amounts of hormone may have are illustrated by the fact that maximal contraction of excised uterus from a virgin guinea-pig has been evoked by Abel's postpituitary tartrate in dilution of 1 to 15,000,000,000. The changes in pigmentation seen in the skin of amphibia deprived of postpituitary hormone are ascribed to loss

of an influence on the melanophores (pigment-carrying organs) which normally causes the pigment to be held near the surface (some investigators think the hormone determines the *amount* of pigment as well as its position in the skin.

The effect of postpituitary hormone on urine formation may be either to cause an increase (diuretic action) or a decrease (antidiuretic action) according to conditions not wholly understood. It appears at present, however, that the *diuretic action* (seen most strikingly when small doses of hormone are administered to anesthetized experimental animals), is to be attributed to an augmented filtration from the glomeruli of the kidneys, which results, in turn, from heightened glomerular blood-pressure. The action of the hormone is interpreted as being that of causing increased contraction of the *efferent vessels* of the glomeruli, which would necessarily heighten glomerular blood-pressure (page 355). Assuming no change in reabsorption diuresis would inevitably follow increased filtration.

The *antidiuretic action* is attributed to a specific stimulating effect of the hormone on the tubule cells concerned with reabsorption, causing them to take up water more actively in the presence of the hormone than in its absence or too great dilution. The action is utilized clinically as a means of reducing the excessive urine flow of *diabetes insipidus*, a disease characterized by formation of abundant and very dilute urine (page 438), probably the result of insufficient reabsorption of water. It is conceivable that in diabetes insipidus a larger proportion of glomeruli than normal are functioning simultaneously, and that postpituitary hormone may have the further effect of reducing the number of functioning glomeruli to somewhere near normal (page 356). The proportion of salts in the urine is altered in consequence of administration of postpituitary extract (Stehle), indicating that the hormone influences the action of the tubule cells on salts as well as on water.

Injection of postpituitary extract into lactating women or experimental animals causes a surprisingly large increase in milk yield. Whether this is due to a stimulating effect of the hormone on the milk-secreting cells or is simply an increased out-pouring of milk already formed cannot be said with certainty, although the weight of present evidence seems to favor the latter. Repeated injections of hormone-containing extracts maintain augmented milk flow for a time, although with steadily lessening effectiveness. Furthermore, when the secretion of milk is deficient administration of postpituitary extract is of little or no benefit. The action of the extract in causing conversion of glycogen to sugar appears to be in direct antagonism to the action of insulin (G. A. Clark).

Hormones of the Anterior Lobe of the Pituitary.—The anterior lobe of the pituitary is derived as an out-growth of the buccal

epithelium. It has been definitely shown to produce at least two distinct types of hormones (Evans and co-workers), one functioning mainly as a stimulator of growth (perhaps with some influence on general metabolism as well), the other as a modifier of ovulation (page 753). Young animals deprived experimentally of anterior lobe remain small. The most striking failure of growth is in the skeleton, although other tissues are affected as well. Administration of anterior lobe, preferably by injection, although some satisfactory results have been obtained by feeding the extracts, stimulates growth in young animals materially. In one experiment a rat thus treated grew to twice the weight of its normal litter-mate control. Part of the increase was attributable to augmented fat deposition, but there was also marked enlargement both of the skeleton and of many soft organs. A disease of the young in which the anterior lobe is believed to be over-active (*hyperpituitarism*) results in excessive growth, particularly of the long bones, giving rise to *gigantism*. A corresponding disease in adults, coming on after ossification is practically complete, is characterized by over-growth (hypertrophy) of the bones of the face and enlargement of the bones of the extremities near the joints. This condition is known as *acromegaly*.

If transplants of living anterior pituitary tissue are made daily into the bodies of young female rats sexual maturity comes on very much earlier than in normal controls (Philip Smith). On the other hand administration of anterior lobe extract to adult female experimental animals hinders or even suppresses ovulation together with the accompanying phenomenon of heat (œstrus). When continued throughout life the ovaries hypertrophy and display many substantial corpora lutea, but no ripe Graafian follicles (page 751). The uterus, on the other hand, remains small in comparison with normal animals (Evans and Long).

A disease of human beings (Frœlich's syndrome) is clearly associated with hypofunction of the pituitary body. The main symptoms, retardation of skeletal growth, sexual infantilism and obesity, indicate the failure to be chiefly of the anterior lobe, but the diabetes insipidus which is also often seen suggests involvement of the posterior lobe as well. That more is involved than simple hormone lack is indicated by the fact that administration of pituitary extracts has little or no beneficial effect. Removal of the entire pituitary in experimental animals leads to a condition (cachexia hypophyseopriva) signalized by a general lowering of the level of basic metabolism. The symptoms include increasing weakness and sluggishness, and lowering of body temperature, culminating in death in about three days.

Hormone of the Pineal Body.—The pineal body, which arises as an evagination of the third ventricle, is generally looked on as an endocrine gland, although the evidence to this end is by no means

satisfactory. Extracts of the pineal body produce no characteristic effects so far as anyone has yet observed. There is clinical evidence, however, that in young children injury to or destruction of the gland, resulting in *hypopinealism*, is followed by abnormally rapid growth, and particularly by early and rapid development of the sexual organs and the secondary sexual characters, leading to precocious puberty. In normal individuals there is evidence of retrogressive changes in the gland after puberty. The interpretation usually made is that the pineal hormone acts to prevent the sex glands from developing early in life, before the body as a whole has reached a state of development fitting it to take on the reproductive function.

Hormones Associated with the Reproductive Process.—There is evidence for the existence of a number of hormones associated with the various stages in the development and functioning of the organs of reproduction. It is probable that in man hormones control or regulate every stage, from the determination of sex in the early developing embryo; through the phenomena of puberty, characterized by the development of functional gonads and by the appearance of secondary sexual characters; then through the actual phenomena of reproduction, *i. e.*, œstrus (heat), ovulation, impregnation, implantation of the fertilized ovum, parturition and lactation; to final termination in the menopause (cessation of sexual activity). In addition to these special functions associated with reproduction there is world-old knowledge, derived from observations on castrated males and spayed females, that some of the hormones concerned with reproduction (specifically those of the interstitial or *puberty gland*, page 748) have a general influence on metabolism. This is evidenced in many ways. The flesh of castrated animals, for example, differs in flavor and in proportion of fat from that of non-castrated animals of the same species and age reared under similar conditions. There are differences in central nervous functioning, seen in cattle in the fierceness of functional males and the strong maternal instincts of functional females, as contrasted with the mildness and indifference of sterilized individuals. (For discussion of the relation of these hormones to reproduction, see Chap. XLI.)

The Adrenal Cortex.—This organ is both embryologically and physiologically distinct from the adrenal medulla. It is included by practically all authors among the endocrine glands, although there is no actual evidence that it produces a hormone, and only vague suggestions as to its possible function. One fact regarding it stands out with remarkable clearness, namely, that animals deprived of cortical tissue, without injury to other important structures, appear to get along normally for a time, but sooner or later suffer a sudden and fatal breakdown. The chief symptoms attending the breakdown are marked muscular weakness and lower-

ing of body temperature. Both of these suggest an acute lessening of the basic metabolism. Certain investigators (Aschoff) have been impressed with the high cholesterol content of the adrenal cortex, a concentration which increases in the human mother during pregnancy, and with a pronounced resorption of cortical material, including its cholesterol content, which occurs in infants shortly after birth. They have deduced from these findings a connection of the cortex with cholesterol metabolism. In Chapter II, page 37, there is mention of the probable importance of cholesterol as a constituent of protoplasm. The essential view of this group of investigators is that the adrenal cortex regulates cholesterol metabolism, and that this metabolism is so bound up with the fundamental metabolism of some tissues, probably those of the central nervous system, that any serious disturbance in cholesterol equilibrium results fatally. Addison's disease, characterized by muscular weakness, low blood-pressure, gastro-intestinal disturbance and a peculiar bronzing of the skin, due to an increased deposition of the pigment, melanin, is generally attributed to injury to the adrenal cortex. No satisfactory explanation of these symptoms in terms of cortical function has yet been made.

Interrelations Among the Endocrine Glands. Much attention has been directed to changes found to occur in some endocrine glands as the result of over- or under-activity of others. For example, after removal of the thyroid the anterior lobe of the pituitary becomes altered in appearance and much enlarged. Similarly, the adrenal cortex hypertrophies after removal of the puberty gland by castration. Facts of this kind indicate an interrelation among the endocrine glands. The suggestion has often been advanced that the relationship is compensatory; that is, deficiency in one hormone is made up for by over-production of another. It is probable that in some cases this is true. An important point to bear in mind, however, is that the changes in cell environment which are wrought in the endocrine glands, in common with all other bodily tissues, by over- or under-production of one or another hormone are likely to result in changes in the metabolism of the cells, whether or not the changes are useful to the body at large. One is not justified in assuming that because interrelations of this sort exist they are necessarily useful. Each case must be established by individual study.

Summary.

Vitamins (with one exception) are synthesized by plants, and taken into the bodies of animals in their food. They influence metabolism in various ways. Almost nothing is known, as yet, as to the quantities of individual vitamins present in the body, the details of their action, nor the manner and rate of their elimination

or destruction. They fall chemically into two distinct classes. Vitamins A, D and E are non-nitrogenous, and belong to the category of sterols; vitamins B, C and bios are nitrogenous, and thought to be amines.

Vitamin A, a sterol, is found in actively growing parts of plants, and as a fat-soluble compound in glandular and adipose tissues in animals, and in high concentration in milk, egg-yolk and fish-liver oil. Vitamin A must be present if the body is to avoid going into a nutritive decline, likely to culminate in death. In A deficiency there is marked susceptibility to infection, particularly to xerophthalmia. There is also failure to grow on the part of young animals.

Vitamin B, a water-soluble amine, prevents beriberi (polyneuritis), promotes growth and stimulates the appetite. It is present abundantly in yeast, in the embryos and hulls of grain and in the green parts of plants. Endosperms are wanting in B. Eggs and milk contain B provided the diet of the egg-laying or lactating organism provides it. There is little storage within the animal body.

Vitamin C is a water-soluble antiscorbutic amine. It is present abundantly in juicy fruits and vegetables and in leaves, growing shoots and sprouting grain. Less watery fruits and vegetables contain smaller, but still considerable amounts. Roots and mature seeds are nearly devoid of it. Animals have C in their bodies and secrete it in their milk when on a diet in which the vitamin is present.

Vitamin D is an antirachitic sterol occurring in cod-liver oil. It may be produced in inactive fats by irradiating them with ultraviolet light. This latter fact appears to account for the beneficial effects of direct exposure to sunlight in cases of rickets. The fats "activated" in these cases are those circulating in the blood, in other words animal fats; this vitamin is, therefore, an exception to the rule that vitamins are synthesized by plants.

Vitamin E is a sterol which maintains fertility. In its absence the germinal tissues develop abnormalities; growing embryos also undergo resorption after a period of apparently normal growth. E is present as a fat-soluble constituent of yellow corn, wheat germ and hemp seed; it also occurs in lettuce, dried alfalfa and some other foods.

Bios is an amine synthesized by yeast plants and effective in promoting the growth of yeast. It resembles vitamin B, but is thought not to be identical with it. It has not been shown to have any vitamin-like action on the animal body.

Hormones are synthesized for the most part by specialized tissues making up the *endocrine glands*. They influence metabolism in a variety of ways. Some appear to be general in action, affecting the metabolism of all cells with which they come in contact. Others seem to affect only certain tissues or particular bodily processes.

Thyroxin, an iodine compound of hydroxyphenoxyphenylaminopropionic acid, appears to function as a hydrogen acceptor and transporter, and hence as a regulator of physiological oxidations. The effect seems to be quantitative, 1 mg. of thyroxin leading to the production in the body of approximately 1008 Calories. The action is gradual, coming to a peak in about eight days, and lasting about twenty days.

Hyperthyroidism of transient character is induced by administering thyroxin, pure or as thyroid extract. In chronic hyperthyroidism over-activity of the thyroid gland is involved. The symptoms are such as attend a general heightening of the level of basic metabolism.

A condition occurs in human beings indicative of *aberrant thyroid function*. The symptoms resemble those of hyperthyroidism, but differ enough to indicate the possibility that a hormone is being produced with less than 4 atoms of iodine to the molecule, hence more active, and perhaps specifically injurious as well.

Hypothyroidism may be due either to congenital deficiency of thyroid substance (cretinism), to loss of thyroid tissue through atrophy, degeneration or operative removal (myxedema) or to insufficient quantities of iodine in the diet (endemic goiter). The effects on the body are such as result from general lowering of the level of basic metabolism. Relief from cretinism and myxedema may be had through the administration by mouth of thyroxin or thyroid extract; endemic goiter is alleviated by including iodides in the diet.

Parathyrin, the hormone of the parathyroid gland, has to do with calcium metabolism. Increases in parathyroid content of the blood bring about increases in blood calcium. Parathyroid tetany results from deficiency in parathyrin. The acute attacks appear to be precipitated by materials of protein origin absorbed from the alimentary tract. Parathyrin injection protects the organism completely against tetany. Over-dosage with parathyrin leads to *hypercalcemia*, which in turn may, if excessive, cause death.

Adrenin, or *epinephrine*, is the hormone produced by the chromaffin tissues. These are located chiefly in the adrenal medulla. Adrenin is secreted under nervous excitation. There appears to be continual slight excitation, so that there is a steady out-pouring of the hormone in minute amount into the blood. The normal concentration in arterial blood is of the order 1 to 500,000,000 to 1 to 1,000,000,000. Stimulation of the splanchnic nerves causes a much more abundant secretion. Destruction is prompt. It is probable that individual molecules function only once, or at most a few times.

Little evidence exists for function of adrenin as it is normally present in the blood. In higher concentration adrenin has the property of stimulating all tissues that are innervated through the

sympathetic subdivision of the autonomic system. The sign of response is the same as in nervous stimulation itself. Other actions are mobilization of sugar, hastening of the clotting of blood, and counteracting fatigue of myoneurol junctions. Adrenin is secreted actively during muscular exertion and also during emotional excitement. The physiological effects are such as to suggest that adrenin functions largely as an "emergency" hormone.

Insulin, the hormone of the islands of Langerhans, lowers the glucose tension of the tissues and inhibits the conversion of glycogen to glucose and of fats to carbohydrates. The adequate stimulus to secretion of insulin appears to be a blood-sugar concentration in excess of about 0.12 per cent. Nothing is known as to the normal concentration of the hormone in the body. It is destroyed or eliminated rather rapidly. The hormone property is associated with the presence of "labile" sulphur in the molecule.

The posterior lobe of the pituitary body produces a *postpituitary* hormone (or group of hormones) which acts as an excitant of smooth muscle and allied contractile cells, causing a rise of arterial blood-pressure, contractions of uterus, intestines and bladder and pigment shifts in the melanophores of amphibia. The diuretic action of the hormone is explained as due to a rise of blood-pressure in localized kidney vessels. The hormone has an antidiuretic action thought to result from a stimulating effect on the reabsorption of water by the cells of the kidney tubules. The galactagogue action is thought to be a stimulation of out-pouring of milk already formed, rather than the evoking of increased secretory action in the mammary gland cells.

The *anterior lobe* of the pituitary produces two distinct hormones or groups of hormones, one functioning mainly as a stimulator of growth and the other to modify sexual processes in the female. Deprivation of anterior lobe hormone in the young results in failure of growth, seen most strikingly in the skeleton. Over-activity leads in the young to *gigantism*, in adults to localized hypertrophy of bones (acromegaly). Daily transplants of anterior lobe substance greatly hasten sexual maturity in female animals. Administration of anterior lobe extract to adult female animals on the other hand hinders or suppresses ovulation and œstrus.

Removal of the entire pituitary results in progressive lowering of the level of metabolism and shortly in death.

The *pineal body* is thought to produce a hormone whose action is to restrain development of the sexual apparatus until the body as a whole has had time to attain a state in which it is fit to take on the reproductive function.

There is evidence for the existence of several hormones produced by endocrine glands immediately associated with the sex organs. These hormones function specifically in connection with reproduc-

tion. The hormone of the *puberty* gland appears to have also a general influence on metabolism.

The *adrenal cortex* is thought to be an endocrine gland. Its removal is fatal to the organism. The breakdown is acute, suggesting a sudden lowering of the level of basic metabolism. Some investigators have suggested cortical function to be related to cholesterol metabolism. There is evidence that Addison's disease is due to impairment of function of adrenal cortex.

The various endocrine glands are definitely interrelated. The biological significance of this fact is not clearly established. In some cases the relationship appears to be compensatory.

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CHAPTER XIII.

CELL ENVIRONMENT: OXYGEN.

Oxygen in Tissue Fluid.—Oxygen is the final hydrogen acceptor, so far as known, for all oxidations occurring in the tissues of higher organisms (page 50). Since the energy for most metabolic processes is derived through oxidations it follows that the demand of the cells for oxygen is continuous and insistent. Thus far no experiment has shown animal cells to have any storage capacity for oxygen. The evidence indicates that oxygen enters the cells in quantities just sufficient to meet their metabolic demands. So far as individual cells are concerned, the source of oxygen supply is in the immediately surrounding tissue fluid. Oxygen is only slightly soluble in water and even less soluble in a liquid having the composition of tissue fluid.

The factors determining the quantity in solution in tissue fluid and in blood plasma (page 250) as well, are: (*a*) Specific solubility, the more soluble the gas the more will be present under any given set of conditions; (*b*) temperature, the quantity in solution varies inversely with the temperature; (*c*) the pressure of the gas in the overlying atmosphere. The relationship in this last case is direct, and is independent of other gas pressures that may be present at the same time. Thus raising or lowering the oxygen pressure in an atmosphere in contact with a solution causes oxygen to dissolve or escape in exact proportion to the change in pressure, regardless of whether other gases in the same atmosphere remain constant or not. In other words, the *tension* of a gas in solution equals the *pressure* of the same gas in the overlying atmosphere. This is *Henry's law*. The average oxygen pressure in the alveolar air of man (page 368), which is the pressure with which blood plasma and tissue fluids tend to be in equilibrium, is about 13 per cent of an atmosphere (sufficient to sustain a column of mercury 100 mm. high).

Under the conditions prevailing in the tissue spaces of the human body the actual quantity of oxygen in solution is stated (Haldane) not to exceed 0.25 ml. of the gas (measured at 0° C. and 760 mm. pressure) in 100 ml. liquid. While the total amount of liquid in the tissue spaces can be only very roughly estimated (page 158), it is almost certain that it does not exceed 6 liters. From this we can safely conclude that so far as the tissue fluids are concerned the

immediately available oxygen supply for all the cells of the body is not more than 15 ml. The oxygen consumption of the average adult body at rest is at least 300 ml. per minute. It follows that the tissue fluids upon which the cells must draw for their oxygen supplies have not more than four or five seconds' margin. Clearly there must be a source of oxygen from which the tissue fluids can be rapidly renewed. This source, as is well known, is in the circulating blood.

HEMOGLOBIN AS OXYGEN CARRIER.

As a solvent for oxygen blood plasma is in the same category with tissue fluid. Barcroft has made the interesting calculation that if all the oxygen carried by blood were in simple solution in the plasma there would have to be 300 kilograms of the latter, or four times the weight of the whole body. The presence in blood of the oxygen-carrying pigment, *hemoglobin*, makes possible efficient oxygen transport with a relatively small bulk of circulating fluid. As a matter of fact blood, by virtue of the hemoglobin in it, has more than eighty times the oxygen-carrying capacity of plasma.

Hemoglobin (Hb) is a complex water-soluble substance of remarkably high molecular weight. Recent determinations (Adair) indicate a value in the region of 68,000. The basis of hemoglobin is a pigment, not known to exist independently, but very widely present in combination in plants and animals. This pigment has been assigned the name *hem*. It is thought to have the composition represented by the formula $C_{34}H_{35}O_3N_4Fe$. It is very little soluble in water, hence by itself has little utility in the animal body. Hem forms with various nitrogenous substances, a series of *hemochromogens*. The particular hemochromogen of present interest is a compound of hem with the protein *globin*. This compound has an approximate molecular weight of 16,800. Within a definite hydrogen-ion concentration range globin-hemochromogen passes over into ordinary hemoglobin, apparently by molecular condensation, 4 molecules of the hemochromogen condensing into 1 of hemoglobin. Hemoglobin is much more water-soluble than hemochromogen. It also combines reversibly with oxygen (the property which makes it useful as an oxygen-carrier) which its precursor does not. If the view of hemoglobin constitution here presented is correct, each molecule contains 4 atoms of iron, instead of only 1 as formerly believed.

Significance of the Red Corpuscles.—Hemoglobin in solution in water has the property of combining with oxygen to form *oxyhemoglobin* according to the reaction $Hb + O_2 \rightleftarrows HbO_2$. This is a reversible reaction in which equilibrium depends on the quantities of hemoglobin and oxygen present, in accordance with the mass

law. In the animal body the hemoglobin is not in solution in the plasma but is held within the red corpuscles. This fact is significant for at least four reasons: (*a*) The movement of corpuscles through the capillaries is positive, whereas dissolved hemoglobin might stagnate in contact with the capillary walls; (*b*) the concentration in the corpuscles is higher than it could be in the plasma without increasing the osmotic pressure and viscosity unduly; (*c*) the hemoglobin is aggregated in company with electrolytes, chiefly potassium salts, so that the Donnan equilibrium is manifested; (*d*) the hydrogen-ion concentration inside the corpuscles is slightly higher than of the surrounding plasma (page 165).

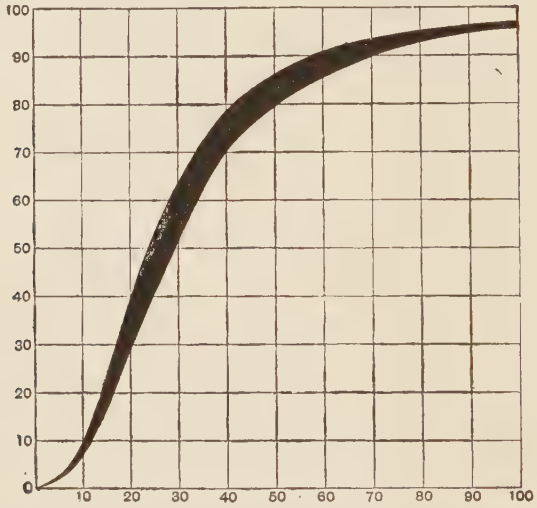

Fig. 23.—The dissociation curve for oxyhemoglobin. Numbers on the base line stand for oxygen tensions in mm. Hg.; on the vertical line for percentage oxygen saturation. (Barcroft's Respiratory Function of Blood, Cambridge University Press.)

The effect of factors, *b*, *c* and *d*, is to make the conditions of equilibrium between Hb and HbO_2 in the reaction given above different in blood from those that obtain in solutions of hemoglobin in water. We shall concern ourselves here only with the conditions that prevail in blood. Other factors being constant (the average situation obtaining in blood is assumed for these), the equilibrium depends on the quantity of oxygen present. Expressing the oxygen in terms of tension (page 214), and the oxyhemoglobin in percentage of the total original quantity of hemoglobin, the relationship gives the curve shown above (Fig. 23). To allow for individual differences in hemoglobins, which are important because they affect the equilibrium between Hb and HbO_2 at different oxygen tensions,

the curve is broad, instead of being a sharp line. It is commonly referred to as the *dissociation curve of oxyhemoglobin.*

Oxyhemoglobin Formation as Affected by Acid in Blood.—In discussing the buffer action of the blood (page 164) reference is made to the fact that considerable amounts of carbonic and other acids can be carried in the blood without much change in hydrogen-ion concentration by virtue of the capacity of the red corpuscles for acid. It is exceedingly interesting as well as significant that this capacity for acid is at the expense of the oxyhemoglobin-forming property. In other words, the more acid is present the less proportional amount of oxyhemoglobin will be formed at any given oxygen tension. The fact is illustrated graphically in Fig. 24. Each curve represents the equilibrium between unoxidized hemoglobin and oxyhemoglobin, over the range of oxygen tensions from

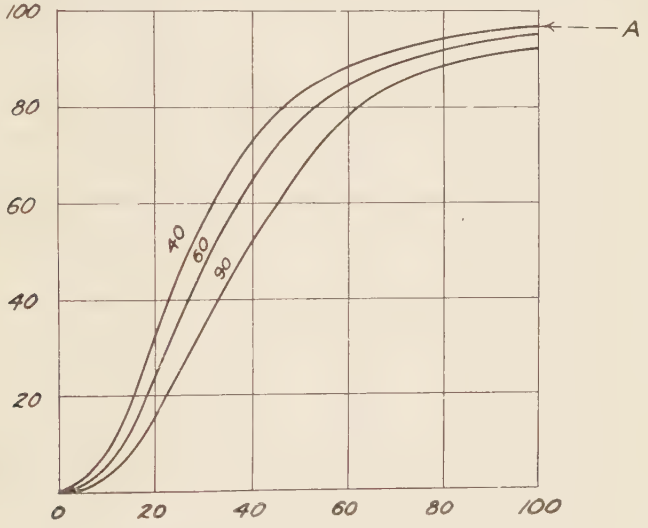

FIG. 24.—Effect of CO_2 on dissociation curve of oxyhemoglobin. Curves are at CO_2 tension of ordinary arterial blood, *i. e.*, 40 mm. Hg.; at CO_2 tension of venous blood, *i. e.*, 60 mm. Hg.; at CO_2 tension of excessively venous blood, *i. e.*, 90 mm. Hg. Ordinate = percentage saturation; abscissa = oxygen tension. (After Barcroft.)

zero to 100 mm. Hg., at a particular acid concentration determined by allowing the blood to come into balance with a given overlying pressure of carbon dioxide.

Oxygen Transport in the Resting Body.—On the basis of the facts set forth above a summary of the mechanism of oxygen transport can be given as follows: During the passage of the blood through the pulmonary capillaries it is exposed to an atmosphere (alveolar air) in which the oxygen pressure is ordinarily around 100 mm. Hg., at an acid concentration represented by 40 mm. CO_2 tension.

Reference to Fig. 24 (point *A*) shows that under these conditions approximately 97 per cent of the hemoglobin may be in combination with oxygen as oxyhemoglobin. In other words, the hemoglobin may theoretically become 97 per cent saturated. Each milliliter of blood will then contain about 0.185 ml. oxygen (measured at 0° C. and 760 mm. pressure), and the whole body 600 to 650 ml., provided the blood has normal hemoglobin content (page 262), and assuming all the blood to be arterial, *i. e.*, fully charged with oxygen.

During the passage of arterial blood from the pulmonary capillaries to the tissue capillaries there is no appreciable change in oxygen concentration. Any oxidations that occur within the arterial blood stream in man are on too small a scale to be significant (Warburg). The blood enters the tissue capillaries, therefore, carrying the same load of oxygen as when it left the lungs. In the tissue capillaries it comes into diffusion relationship with the tissue fluids. These fluids differ in oxygen tension and carbon dioxide tension in different parts of the body. It appears that in general the oxygen tension is low in resting muscles (30 mm. or less); some higher in glands and nervous structures. The CO_2 tension is somewhat above that of alveolar air (40 mm.), probably between 45 and 60 mm. Under these conditions some of the oxyhemoglobin necessarily decomposes, giving off oxygen to the tissues. Ordinary venous blood is a mixture from all the tissues. Its oxyhemoglobin percentage in the resting body is usually between 70 and 80, indicating, as reference to Fig. 24 shows, an average oxygen tension in the tissue fluids in the neighborhood of 50 mm. This conclusion as to the oxygen tension in the tissue fluids is based on the assumption that the hemoglobin-oxyhemoglobin system comes into full equilibrium. Whether this will actually be the case or not depends on another factor, *i. e.*, that of time. In the resting body the average time spent by any given drop of blood in passing a systemic capillary is estimated at about 1.6 seconds (page 322). In the pulmonary capillaries the average time is probably about the same (page 354). If equilibrium is reached the movement of oxygen must be completed within this time. It has been shown experimentally that in the quiet organism this very nearly happens. Arterial blood has been found to contain in a resting individual about 95 per cent oxyhemoglobin, showing that in the lungs almost as much oxygen is taken up as is theoretically possible. Venous blood is more variable, but, as stated above, commonly contains fully three-fourths as much oxygen as arterial blood. The average withdrawal of oxygen during rest, according to the most recent, and apparently most reliable determinations, does not exceed 0.04 ml. per ml. of blood.

From the facts presented in the above paragraphs it is clear that in the resting body the oxygen demands of the tissues are fully and easily met, provided the circulation of blood does not fail, and pro-

vided the oxygen and carbon dioxide pressure of alveolar air do not depart too widely from 100 mm. and 40 mm. Hg. respectively (page 217).

Oxygen Transport in the Active Body.—When the body becomes active we are confronted with quite a different situation. The increase in oxygen consumption during activity as compared with rest has been determined directly for various tissues, including skeletal muscle and several glands. The greatest increases occur in skeletal muscles, which under experimental conditions have shown more than thirteen-fold multiplication, *i. e.*, from 0.006 ml. to 0.08 ml. oxygen per gram tissue per minute (cited by Halliburton). We have to deal with the possibility, then, that the delivery of oxygen to individual tissues may on occasion rise to a value at least thirteen times as great as usual.

Several factors coöperate to enable this to happen. First and foremost is a prompt and very extensive increase in the quantity of blood flowing through the active tissues per unit of time. In part this is due to a speeding up of the circulation (page 349), and in part to a widening of the capillary bed (page 289), so that the tissue accommodates a greater volume of blood. The increase in velocity of movement may possibly be as great as five-fold or thereabouts. The widening of the capillary bed may be anywhere from two to twenty-fold (page 341). Thus it is conceivable in theory that a tissue may receive anywhere from ten to one hundred times as much blood per second in activity as in rest. It must be noted, however, that the increase in blood flow due to widening of the capillary bed has sharp limitations. If a large mass of tissue is active all at once, as in severe muscular exertion, not enough blood may be available to fill an excessively widened bed to capacity. The total volume of blood is relatively constant (page 271). It follows that increases in amount in one set of tissues involve corresponding decreases in others, and it is clear that no very great mass of tissue can receive even a moderate augmentation in blood content without subjecting other tissues to undue depletion. In effect the situation is that small tissue masses may have their blood supply per unit of time augmented sufficiently to care for their maximal oxygen requirements through this means alone. Larger masses obtain less, the delivery of blood falling farther and farther below the theoretical maximum the more nearly the mass of active tissue approximates becoming a major portion of all the tissue in the body.

Under the favorable conditions prevailing in small tissues, as just pointed out, increased oxygen consumption due to activity may be fully cared for by the increased blood supply, so that drop for drop of blood no greater percentage dissociation of oxyhemoglobin is called for during activity than during rest. It is true,

however, that the dissociation must be quicker. On account of the speeding up of the circulation each drop of blood is in its capillary less time than formerly, and so has less time in which to unload an equal quantity of oxygen. To explain the more rapid escape of the gas we have to consider what is happening in the active tissue. At the outset there will clearly be a drawing upon the immediately surrounding tissue fluids for more oxygen than formerly, and as the result of the increased oxidations a greater yield of CO_2. The tissue fluids thus become at once much poorer in oxygen and richer in CO_2. A steeper diffusion gradient for oxygen from blood to tissue fluid is established, favoring a more rapid discharge of the gas. Furthermore, the rise in CO_2 tension sets the equilibrium point for oxyhemoglobin at a lower level (Fig. 24) and so promotes release of oxygen.

In case the mass of active tissue is so great that the increase in blood supply does not equal the increase in oxygen demand, it is still possible to bring the oxygen delivery up by increasing the amount of oxygen contributed by each drop of blood. In the last paragraph the fact is noted that the tissue fluid becomes poor in oxygen during activity. As a matter of fact the oxygen tension may drop nearly or quite to zero. Reference to Fig. 24 will show that under this circumstance the percentage of oxyhemoglobin at equilibrium falls very low. In other words, oxyhemoglobin tends to give off nearly all its oxygen. Conditions are thus favorable for as large an output of oxygen as the brief stay of given drops of blood in the capillaries permits. That the latter is still a limiting factor is shown by the observation that even in severe exertion involving many muscles the venous blood is found to contain considerable oxyhemoglobin (nearly one-third saturation; Lundsgaard and Miller).

In Chapter VI, page 91, the fact is brought out that muscular metabolism may, and often does, outstrip the utmost ability of the circulation to deliver oxygen to the laboring tissues, so that they "go into debt for oxygen." This can happen because the contractile activity proper is anaërobic, the utilization of oxygen occurring in connection with "recovery oxidation." The fact that a tissue is going into debt for oxygen is signalized by the out-pouring of sodium lactate from it into the blood (page 91). This lactate circulates about the body, and as it passes through regions poor in lactates diffuses from the blood into the tissue cells. If oxygen is available, in excess of the immediate metabolic requirements of these cells they oxidize a portion of the lactate (or other available fuel, page 88) and through the energy thus made available resynthesize the remainder of the lactate into glycogen. The effect of this is that all the muscle cells and conceivably most or all the cells of

the body take part in the oxidations incidental to vigorous muscular work.

In view of this wide participation of the cells it is clear that in the body as a whole the limit to oxygen consumption is set by the capacity of the blood to take up oxygen in the capillaries of the lungs. This capacity depends on the volume of blood flowing through the pulmonary capillaries per unit of time, assuming the pressure of oxygen in alveolar air to be maintained at a level sufficient to saturate the hemoglobin (page 217). In actuality, the transport of oxygen falls below the theoretical maximum both through failure of the hemoglobin to take up oxygen to saturation and through its failure to give off all its load. In very severe exertion, when the blood is moving at maximal velocity through the pulmonary capillaries the percentage of oxyhemoglobin may drop to 93 or below. The quantity of blood passing through the vessels of the lungs per minute during active exercise may be as high as 36 to 38 liters in a large and powerful man (page 348). If the hemoglobin in this quantity of blood becomes 93 per cent saturated with oxygen each milliliter of hemoglobin will contain about 0.17 ml. O_2, and the maximum amount that might be taken up will be between 6 and 6.5 liters. Probably the largest recorded actual consumption of oxygen in one minute in man is 4.6 liters (Y. Henderson), observed in an oarsman during intense exertion. The difference between 4.6 and 6.5 liters represents roughly the inefficiency of oxygen transport due to failure of the hemoglobin to give off all its load.

ANOXEMIA.

We have considered the oxygen supply to the tissues in rest and in activity, but in both cases on the assumption that the quantities of oxygen essential to their normal functioning are brought to the tissue capillaries by the blood stream. There remain the further inquiries as to what are the effects of inadequate oxygen supplies, and what are the conditions in which the supplies tend to become inadequate.

Any tissue that is failing to obtain the quantities of oxygen needed for its normal oxidative processes is said to be suffering from *anoxemia*, or oxygen-want. In both basic and functional metabolism oxidations are links in complex reaction chains; it follows, therefore, that decreases in the amount of oxidation may go further than merely lower the general level of metabolism, and operate to bring about profound changes in fundamental cell chemistry. Space does not permit extended description of the effects of anoxemia. The simplest in theory, although not often seen in practice, is the sudden loss of consciousness that follows taking 10 to 30 breaths of an "indifferent" gas, like pure nitrogen. Here acute

anoxemia is momentarily induced; the oxygen tension of alveolar air quickly falls to zero, and as quickly returns to normal. The tissues are deprived of oxygen for only a short time and recovery is prompt and complete. By various means to be discussed presently long-continued partial anoxemias may be established. The effects of these are in proportion to the severity and duration of the oxygen-want. There may be merely a dulling of the senses, the intellect, and the judgment with marked "fixation of ideas;" or there may be pronounced depression together with gastro-intestinal disturbances, as seen in "mountain sickness" (page 223); in severe cases epileptiform seizures, partial paralysis and coma may occur; if the anoxemia is prolonged cardiac, renal and other symptoms develop. It is noteworthy, as Paul Bert pointed out nearly fifty years ago, that whether the organism as a whole succumbs to accident or disease the death of the general tissues is practically always due to anoxemia.

Causes of Anoxemia.—A cause of anoxemia to which space need not be devoted here is a slowing down of the circulation so that not enough oxyhemoglobin-containing blood to meet the oxygen needs of the tissues passes through the capillaries per unit of time. Return is made to this topic in Chapter XXI, page 351.

Anoxemia may be due also to an insufficient quantity of hemoglobin in the blood. This condition is known as *anemia*, and is dealt with on page 262.

Assuming the circulation to be adequate and the hemoglobin concentration to be normal, anoxemia can only develop from *failure of the blood to take up the usual amount of oxygen* during its passage through the pulmonary capillaries. (In the rare condition of *patent foramen ovale* part of the blood passes directly from the right side of the heart to the left, without traversing the lungs. This blood takes up no oxygen, and of course lessens the oxygen concentration of the arterial blood as a whole. An essentially similar situation may arise within the lungs themselves either through disease or from pulmonary irritation, as in certain types of "gassing." Exudate may collect within some alveoli, some small bronchioles may be occluded, or the alveolar walls may become impermeable to oxygen. In any case blood which passes through the capillaries of non-functioning alveoli fails to be oxygenated. The effect on the arterial blood as a whole is obviously the same as in patent foramen ovale. It appears that in pulmonary affections in which there is consolidation, such as tuberculosis and pneumonia, the above condition does not obtain, because the consolidated areas receive no blood from the pulmonary artery).

Carbon-monoxide Poisoning.—A means of interfering with the uptake of oxygen by the blood is to mix carbon monoxide with the air that is breathed. Carbon monoxide reacts with hemoglobin to form

carbon monoxide hemoglobin (HbCO) in a reversible reaction similar to that between hemoglobin and oxygen. Hemoglobin has, however, two or three hundred times the affinity for CO that it has for O_2. In other words, a CO pressure of 0.4 to 0.5 mm. Hg. is equivalent to an O_2 pressure of 100 mm. Hg. The result is that small concentrations of CO in the air breathed take possession of considerable proportions of hemoglobin, leaving inadequate quantities to combine with oxygen. Serious anoxemia may thus be induced. Since the reaction $Hb + CO \rightleftarrows HbCO$ is reversible, the CO may be dislodged from the blood by breathing a CO-free atmosphere. Expulsion is slow, so that the anoxemia may outlast the acute poisoning for two or three hours. The serious after effects commonly seen in CO poisoning appear to be due to the long-continued anoxemia and not to any specific effects of CO.

Diminished Oxygen Pressure in the Alveoli.—Dwellers at high altitudes, mountain climbers and aviators breathe an atmosphere of which the pressure as a whole, and the oxygen pressure as well, is less than at sea level. The alveolar oxygen pressure (100 mm. Hg. ordinarily), is always less than the oxygen pressure of atmospheric air (152 mm. Hg. at sea level), because lung ventilation is never as complete as is theoretically possible (page 368). The pressure of oxygen in the alveoli at various altitudes, as maintained by the lung ventilation normal to those altitudes, is shown in Fig. 25. If this figure is studied in connection with Fig. 24 it is seen that the decrease in pressure of alveolar oxygen does not become sufficient to affect the uptake of oxygen by the blood to a noteworthy extent until an altitude is reached at which the pressure falls to 60 mm., when the percentage of oxyhemoglobin at equilibrium sinks below 90. An alveolar pressure of 60 mm. corresponds to an altitude of 9000 feet (2750 meters), which, as is well known, is borne without discomfort by nearly all healthy persons. The drop in oxyhemoglobin percentage becomes increasingly more rapid as the alveolar oxygen tension falls beyond this figure. At the altitude of the summit of Pike's Peak (14,100 feet, 4300 meters) the alveolar tension is around 45 mm. and the oxyhemoglobin percentage 80. A considerable proportion of unacclimatized persons develop marked symptoms indicative of anoxemia at this altitude. At 25,000 feet (7600 meters) the alveolar tension is 28 to 30 mm., corresponding to an oxyhemoglobin percentage of 60 to 70 (the alveolar pressure of CO_2 falls at these altitudes, due to over-breathing, page 380; at 25,000 feet it might fall as low as 20 mm., increasing the percentage of oxyhemoglobin as indicated in Fig. 24). Serious anoxemia is inevitable in unacclimatized persons when the oxyhemoglobin percentage falls this low. The matter is of great practical importance in view of the fact that aëroplanes and balloons can ascend to altitudes well above 25,000 feet. It is necessary to provide tanks of

oxygen from which to breathe as high altitudes are reached. Furthermore, since the early effects of anoxemia include depression of judgment and fixation of ideas, but no painful or subjectively disturbing symptoms, it is essential that the aviator be warned to begin inhaling oxygen as dangerous altitudes are approached, regardless of his own feelings or sensations.

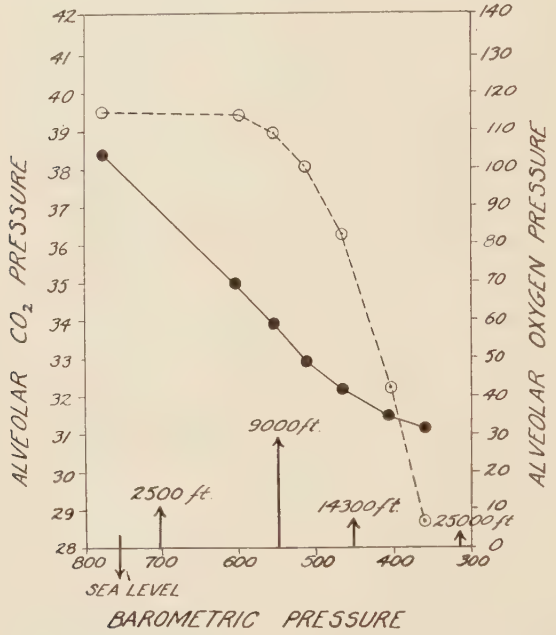

FIG. 25.—Normal alveolar pressures of oxygen and carbon dioxide at various altitudes. Continuous line, oxygen pressure; dotted line, carbon dioxide pressure. (After Boycott and Haldane.)

Acclimatization.—In various parts of the world people live and carry on arduous physical labor at altitudes of 14,000 feet (4300 meters) and over, with relatively little indication of anoxemia. This has been shown (Barcroft *et al*) to be due chiefly to a marked increase in the oxygen-carrying power of the blood. Two factors coöperate to bring this about. One is an increase in the amount of hemoglobin, which may be as great as 50 per cent; the other is a decrease in the acidity of the *inside of the corpuscles* which, as reference to Fig. 24 shows, increases the oxyhemoglobin percentage at equilibrium. Actual tests on the blood of dwellers at altitudes around 14,000 to 15,000 feet show their oxyhemoglobin percentage to be as high as 86, although the oxygen and CO_2 pressures of their alveolar air would not ordinarily permit oxyhemoglobin percentages above 80. That the inside of the corpuscles is less acid

than the surrounding plasma has been demonstrated experimentally. These acclimative changes develop rather rapidly and appear to be promoted by physical exercise. The bases for this idea are the familiar observations: (1) That individuals in "training" suffer much less from anoxemia at high altitudes than untrained persons; (2) that those who climb mountains on foot usually suffer less than persons who ascend on the backs of animals or in vehicles.

THE EFFECTS OF HIGH ALVEOLAR PRESSURES.

Divers and workers in caissons breathe an atmosphere in which the gas pressures are much above those of ordinary air. Divers work regularly at depths of 35 fathoms (210 feet) under a total pressure of 6½ atmospheres (4800 mm. Hg.). A few successful dives to depths of 50 fathoms (300 feet), at 9 atmospheres pressure, are on record. Provided sufficient quantities of air are furnished, there is no immediate trouble either from CO_2 or oxygen at these high pressures. There will be more of the latter gas in solution in the plasma, according to Henry's Law (page 214), and the oxyhemoglobin percentage will presumably be 100, but the tissues are not affected, since the additional quantity in solution in plasma is at most only a fraction of the total quantity present in the blood, on which the tissues are constantly drawing. Prolonged exposure to high oxygen pressures results in inflammation of the lung membranes. This appears to be a directly poisonous action of excessive oxygen on protoplasm. The alveolar linings are not protected as are the tissues which receive oxygen through the blood; these unprotected tissues are the only ones to suffer.

The serious consequences of exposure to high barometric pressures as ordinarily seen are due almost wholly to the greatly increased uptake of nitrogen gas. In accordance with Henry's Law, the amount in solution in the plasma increases as the nitrogen pressure in alveolar air rises. Thus diffusion gradients for nitrogen are set up from plasma to tissue fluids, and thence into the cells themselves. Nitrogen is about six times as soluble in fats as in water. Accordingly the adipose tissues and the myelin sheaths of the nerve axons become particularly heavily charged. The process of diffusion into the tissues is gradual. When the barometric pressure is lowered (decompression) the ability of plasma and tissues to hold nitrogen in solution is reduced, and if the pressure is lowered rapidly the nitrogen is released in the form of bubbles both in the tissues and in the blood stream. The seriousness of the consequences depends on the size, abundance and location of the bubbles. If set free in the small vessels which nourish regions of the brain on which the immediate maintenance of life depends, death is likely to be sudden. Bubbles in the myelin sheaths are thought to account for the pain

and other nervous symptoms characteristic of "caisson disease" and "divers' paralysis." To prevent the formation of bubbles the decompression should be, in theory, so gradual as to permit the nitrogen to diffuse backward, from plasma to alveolar air, and from tissues to plasma, in exact pace with the lessening solubility of the gas. In practice this is not feasible nor is it necessary. A system of decompression in stages, with brief waits at each stage, has been found to prevent all development of symptoms, and at the same time enable divers to reach the surface from extreme depths in about one-half hour. However, in order for this to be true the stay at great depths must be short—twelve to fifteen minutes is the maximum ordinarily allowed. This is to minimize diffusion of nitrogen into the tissues, which, if permitted to go to saturation (a matter of five hours' exposure) would require at least a day for decompression. Helium gas is much less soluble than nitrogen and is fully as "inert" physiologically. A great improvement in diving practice has consequently been secured by supplying divers with an atmosphere of mixed oxygen and helium. The hazards attending decompression have thus been greatly reduced.

Summary.

The cells have no storage capacity for oxygen. They draw continuously upon the immediately adjoining tissue fluids. The oxygen present in these is in simple solution. The *tension* of dissolved oxygen tends to equal the *pressure* of the same gas in the alveolar air, in accordance with Henry's Law. The solubility of oxygen is so small that the actual quantity in solution does not exceed 0.25 ml. oxygen in 100 ml. liquid, or for the whole amount of tissue fluid not more than about 15 ml.

The oxygen needs of the tissues, which are usually not less than 300 ml. a minute in adults, are met through the oxygen-carrying power of hemoglobin. By virtue of the presence of this pigment blood has about eighty times the oxygen capacity of simple plasma.

Hemoglobin (Hb) is a complex iron-containing compound of high molecular weight. Within a definite hydrogen-ion concentration range it forms spontaneously (probably by molecular condensation) from its precursor *hemochromogen*. The latter is a compound of a pigment, *hem*, with globin. Oxidized hemoglobin is oxyhemoglobin (HbO_2).

By virtue of the fact that the hemoglobin is all held within the red corpuscles, the equilibrium conditions in the reversible reaction, $Hb + O_2 \rightleftarrows HbO_2$, are not the same as in pure solutions of hemoglobin in water. The equilibria at different oxygen tensions are plotted to form the *dissociation curve* of oxyhemoglobin in normal blood.

A factor affecting the $Hb \rightleftarrows HbO_2$ equilibrium is the quantity of acid being carried by the red corpuscles. The quantity of acid is stated in terms of CO_2 tension and dissociation curves are drawn for a series of CO_2 tensions. The percentage of oxyhemoglobin at any given oxygen tension is less, the greater the CO_2 tension.

The blood passing through the pulmonary capillaries tends to come into equilibrium with oxygen at about 100 mm. Hg. tension, and CO_2 at about 40 mm. Hg. tension. The hemoglobin tends, therefore, to become about 97 per cent saturated with oxygen. On account of the rapidity of the blood flow through the capillaries only about 95 per cent saturation is actually attained; each milliliter of arterial blood then contains about 0.185 ml. oxygen.

The average oxygen tension of the tissue fluids in the resting body is probably around 40 to 50 mm. Hg.; the carbon-dioxide tension, 45 to 50 mm. Hg. The approach of the blood to equilibrium with these tensions during its flow through the tissue capillaries is such as to leave the blood passing into the veins in rest with about 75 per cent of its arterial oxygen charge.

Active tissues may consume oxygen not less than thirteen times as rapidly as resting tissues. The primary method of providing this additional supply is through an augmentation of the blood flow. In the case of small tissue masses the augmentation may equal, or even exceed, the increased oxygen demand, so that the escape of oxygen per unit volume of blood may be no greater than during rest. When large masses of tissue are active simultaneously the augmentation of blood flow is proportionally less. To meet the oxygen needs of the tissues in this case there is a greater percentage dissociation of oxyhemoglobin, so that the oxygen tension of venous blood becomes lower than during rest.

The limit to oxygen consumption for the body as a whole is set by the extent to which the blood can take up oxygen during its passage through the pulmonary capillaries. The theoretical maximum uptake per minute is 6 to 6.5 liters of the gas. Even in the severest muscular exertion venous blood continues to hold some oxygen, so that the actual oxygen consumption falls somewhat short of the above figures.

Anoxemia, or oxygen-want, is the result of failure of tissue to receive the quantity of oxygen required to carry on its normal oxidative processes. The resulting effects on metabolism may be profound and serious.

The main possible causes of anoxemia are: (*a*) Excessive slowing of the circulation; (*b*) anemia; (*c*) failure of some of the venous blood to pass through the capillaries of functioning alveoli; (*d*) carbon-monoxide poisoning; (*e*) diminished oxygen pressure in the alveoli.

Carbon monoxide reacts with hemoglobin to form HbCO. The

affinity of hemoglobin for carbon monoxide is nearly three hundred times as great as for oxygen. The result is that relatively minute concentrations of CO take possession of considerable proportions of hemoglobin. The reaction Hb + CO $\rightleftarrows$ HbCO is reversible, so that the CO can be gradually dislodged by breathing a CO-free atmosphere.

Alveolar oxygen pressure is less at high altitudes than at sea level. The normal figures at various altitudes can be plotted to form a curve. The dissociation curve for oxyhemoglobin has such a form that the lessening of alveolar oxygen pressure does not become significant in normal persons until altitudes of 9000 feet (2750 meters) or more are reached. As this level is exceeded the tendency to anoxemia, in unacclimatized persons, becomes progressively greater. At altitudes around 25,000 feet (7600 meters) not enough oxygen can be obtained from atmospheric air to obviate serious anoxemia.

Acclimatization to high altitudes appears to be due in part to an increase in the amount of hemoglobin in the blood and in part to a decrease in the acidity of the *inside of the corpuscles*, whereby the percentage of oxyhemoglobin formed at low oxygen tensions is increased.

Exposure to *high alveolar pressures* makes no great difference so far as delivery of oxygen to the tissues and withdrawal of carbon dioxide from them are concerned. Prolonged exposure to high oxygen pressure may bring about inflammation of the alveolar linings. The serious consequences of short exposure to high atmospheric pressures are due to uptake of nitrogen gas. This gas dissolves in plasma in accordance with Henry's Law, and also diffuses readily into myelin sheaths and adipose tissue fats. The effect of rapidly lowering the atmospheric pressure is to set the nitrogen free in blood and tissues in the form of bubbles. The ill-effects of too rapid decompression are due to these.

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CHAPTER XIV.

CELL ENVIRONMENT: MISCELLANEOUS METABOLITES.

METABOLITES AS FACTORS INFLUENCING METABOLISM.

In the course of both basic and functional metabolism various metabolites are formed. From the standpoint of the cell, these are perhaps all to be regarded as waste products, although, as already pointed out (page 134), many cells have as their special function the formation of substances that are of value to the organism as a whole, whatever may be their significance to the cells that synthesize them. In such a complex body as that of man all soluble metabolites to which the cell membranes are permeable diffuse out of the cells into the surrounding tissue fluids. This diffusion depends on the maintenance of diffusion gradients and, accordingly, cannot go on indefinitely unless further diffusion occurs from the tissue fluids into the blood. Since the blood is limited in volume, it, in turn, cannot act indefinitely as a reservoir for metabolites except as it rids itself of them in one way or another; in the case of waste products this is chiefly by elimination through the excretory organs. The blood is to be thought of as charged all the time with a mixture of soluble metabolites to which all the cells contribute. These metabolites are necessarily carried to all parts of the body in the course of blood circulation; since in all parts the tissue fluids tend to come, by diffusion, into equilibrium with the blood, each cell is likely to have in its environment larger or smaller quantities of all the kinds of soluble metabolites produced anywhere in the body. It is clear that even substances which are primarily and predominantly waste products, to be eliminated as expeditiously and completely as possible, cannot be disregarded as factors that may influence metabolism; whether in the cells in which they are produced or in others to which they may be conveyed by the blood.

INSOLUBLE METABOLITES.

In addition to the soluble products spoken of above there are various metabolites which are deposited out of solution in or near the cells by which they are produced. The deposition may be within the cytoplasm or in the thickened cell wall, or by retraction of the protoplasm may be left outside the cell altogether. It may

be permanent and final or in an equilibrium which allows resorption and subsequent utilization. The materials may be inorganic or organic. Calcium oxalate crystals occur commonly in plant cells. Crystals of calcium sulphate are regularly laid down within the bodies of certain microörganisms. Many forms, ranging from protozoa to mollusca, surround themselves with exoskeletons composed of calcium carbonate or of silicates. In arthropods as a group, and in many other forms as well, chitin, a complex organic material, remarkable for its insolubility, is laid down.

For the most part the insoluble metabolites serve useful functions in that they make up the salient parts of supporting and protective structures. In vertebrates the supporting structures are represented by connective tissues, cartilage and bone; the protective structures by scales, plates, feathers and hair. (Teeth and claws, hoofs and nails, fall in the general category, although mediating more specialized functions.) In vertebrates the materials of which these various structures are composed are synthesized and laid down by cells specialized for the purpose just as definitely as enzymes and hormones are synthesized by gland cells.

The supporting and protective structures in vertebrates contain always a large proportion of organic material. One decomposition product of common occurrence is gelatin, a protein of great interest because its molecule includes no tryptophane, and is hence inadequate in nutrition, either for maintenance or growth. The important inorganic constituents are calcium phosphate and calcium carbonate; magnesium phosphate and calcium fluoride occur also, but in relatively small proportion. The chief repository of inorganic metabolites is in the bones. An analysis of a representative bone gives the following proportions (Heintz):

	Per cent.
Calcium carbonate	9.06
Calcium phosphate	85.62
Magnesium phosphate	1.75
Calcium fluoride	3.57
	100.00

Cartilages sometime become impregnated with lime salts, forming so-called *ossified cartilage*. The lime salts of bone form part of an equilibrium system, as already pointed out (page 174), and thus are subject to resorption in order to make good such lime depletion as occurs in lactation or in the nourishment of the fetus. Furthermore, as is well known, bone structure and cartilage structure may be disintegrated *en masse* through the action of the osteoclasts and chondrioclasts respectively.

SOLUBLE NON-NITROGENOUS METABOLITES.

Metabolism gives rise to a great number of soluble compounds (page 46) only a few of which have been identified. Known *non-nitrogenous* metabolites circulating in solution in the blood include *carbon dioxide* and *water*, the final end-products of bodily oxidations; *sodium lactate*, which, as already pointed out (page 91) appears in the blood whenever the muscles are so active as to "go into debt for oxygen;" salts of *phosphoric acid*, produced in connection with the metabolism of phosphatides and nucleoproteins; salts of *sulphuric acid*, formed mainly in the decomposition of the sulphur-containing amino-acid, cysteine. Under abnormal metabolic conditions the *ketone bodies*, a group of incidental products of fat metabolism, appear also (page 234). *Cholesterol*, referred to earlier (page 37) as a probable constituent of cell membranes, falls in the present category, notwithstanding its slight solubility.

Known *nitrogenous* metabolites include ammonia compounds which are *produced* abundantly, in part from deaminization of amino-acids and in part in connection with the wastage of proteins in basic metabolism (page 60), but *occur in blood* only in small amounts, because promptly converted for the most part into *urea*, the most abundant of the nitrogenous metabolites; the *purine bodies*, end-products of nuclear metabolism; *creatinine* and *creatine*, compounds closely related to one another, produced mainly, if not exclusively, in the metabolism of muscular tissues; *pigments* of bile and urine, end-products of body- and blood-pigment decomposition. These various compounds are discussed in some detail below, except metabolic water, which is considered in another connection (page 157).

Carbon Dioxide.—This is the most abundantly produced of all metabolites save water if measured in terms of number of molecules. In terms of gas volumes the daily output will rarely fall below 300,000 ml., and usually rises much above that figure. In Chapter X, page 163, space is devoted to the significance of carbon dioxde in relation to neutrality preservation. It is there pointed out that the maintenance of neutrality depends, in the main, on the elimination of carbon dioxide from the body as fast as formed. The channel of elimination is from the blood into the alveolar air (page 364). A large amount of evidence supports the view that the mechanism of elimination is simple diffusion through the walls of the pulmonary capillaries and the pulmonary epithelium. The blood entering the pulmonary capillaries comes direct from tissue capillaries in which it has tended toward carbon-dioxide equilibrium with the cells and tissue fluids. While the blood is in the tissue capillaries the reactions outlined on page 164 occur. As the result

of these reactions there is an increase in the amount of $NaHCO_3$ and HCl, the latter substance being taken up by the red corpuscles. There is also considerable combination of carbonic acid with reduced hemoglobin to restore the degree of acidity lost in the dissociation of the quite strongly acid oxyhemoglobin. There is finally a certain transport of carbonic acid in simple solution in the plasma, in relation with the plasma buffers. The total quantity of carbon dioxide in venous blood is about 50 to 55 ml. per 100 ml. blood. The amount is determined by the CO_2 tension of the tissue fluids, which, as already stated (page 218), is probably 45 to 50 mm. Hg.

The CO_2 tension of alveolar air is ordinarily around 40 mm. Hg. (page 224). The venous blood entering the pulmonary capillaries is thus brought into the presence of a CO_2 tension lower than its own by 5 to 10 mm. Hg. The lung membranes are freely permeable in CO_2, hence the CO_2 gradient is sufficient to promote diffusion outward of CO_2. This diffusion lowers the CO_2 tension of the plasma and so upsets the previously existing equilibrium. The reactions by which the blood takes up CO_2 in the tissue capillaries are all reversed. A prominent factor is the change of hemoglobin to oxyhemoglobin, whereby the acidity of the blood tends to be increased. This tendency is offset by the escape of CO_2 into the alveolar air. The net result is that as much CO_2 leaves the blood in the lungs as enters it in the tissues. In the normal resting body the amount is around 240 to 260 ml. per minute. The CO_2 remaining in arterial blood averages, in the resting body, about 45 to 50 ml. per 100 ml. blood.

Alkalosis and Acapnia.—It is important to note that the balance between CO_2 production and CO_2 elimination is not always exact from moment to moment. By simply increasing the lung ventilation (page 379) it is easy to lower the CO_2 pressure of the alveolar air much below 40 mm. Hg. The CO_2 gradient becomes correspondingly steeper, leading to a "blowing off" of the CO_2 from the blood. The most important effect is a pronounced reversal of reaction (4) (page 164). In reversed form this reaction is written: $NaHCO_3 + HCl \rightleftarrows H_2CO_3 + NaCl$. With the decrease in the quantity of H_2CO_3 attending the elimination of CO_2, there is a giving off of HCl from the corpuscles, a reaction of this acid with bicarbonate, and so the formation of more H_2CO_3 to be decomposed in turn, with the setting-free of more CO_2. The net result is a *decrease* in the quantity of both $NaHCO_3$ and H_2CO_3 in the blood. The equilibrium is such that the concentration of H_2CO_3 falls off a little more rapidly than the concentration of $NaHCO_3$. Since the actual hydrogen-ion concentration depends on the *ratio of acid to bicarbonate* (page 167), this means a shift in CH in the alkaline direction. The significant fact in this connection is that while the absolute quantity of $NaHCO_3$ in the blood becomes less the *relative* concen-

tration is increased. This condition constitutes *alkalosis*. The body ordinarily adjusts itself gradually by means of a lessened ammonia production in the kidneys (page 148), so that instead of conserving bases by substituting ammonia for them the bases themselves are allowed to escape in the urine. There is also a cutting down of the proportion of unbalanced acid eliminated by the kidneys. The hydrogen-ion concentration of urine shifts in the alkaline direction; often to the alkaline side of neutrality. By this means the normal ratio of acids and bases is restored, but at a lower level of absolute quantity.

A fact of great interest is that characteristic symptoms develop in response to the lowering of the carbonic acid-bicarbonate level in the manner just described. Anyone can induce some of these symptoms in himself by simply breathing quickly and forcibly for a minute or so, until he has swept a considerable volume of CO_2 out of his system. They include a curious light-headedness, and if pushed to excess, loss of consciousness preceded by a feeling that the body is about to float away into space. There is diminution or even suspension of spontaneous breathing (page 380), also depression of functional activity in the gastro-intestinal tract, and diminution of the "relaxing power" of the heart (Y. Henderson). The skeletal muscles may be thrown into intense contractions, a state designated as *tetany*. Both the muscle cramps to which many persons are subject and the convulsive seizures of epilepsy are thus accounted for. The symptoms are related to the lowering of the CO_2 concentration of the blood, a condition given the name of acapnia (CO_2 shortage). After a period of acapnia the body will ordinarily gradually regain the normal level of carbonic acid and bicarbonate because the lung ventilation will not quite keep pace with the production of CO_2 by the tissues; the alveolar CO_2 tension will rise and thus the blood will regain its former state. The process may be hastened by including a small concentration of CO_2 in the air breathed.

Carbon Dioxide Excess.—A great increase in the carbon dioxide production of the body accompanies and follows vigorous muscular exercise. The effect would be to raise the carbonic acid level of the blood. As a matter of fact this does not ordinarily happen, except to a slight extent, because the increase in the circulation (page 349) and in lung ventilation (page 376) eliminates the carbon dioxide virtually as fast as produced. An actual large excess can be established experimentally by causing animals to breathe an atmosphere containing CO_2 at 40 mm. Hg. pressure or more. The oxygen pressure should be not less than 100 mm. Hg. in order that anoxemia may not complicate the symptoms. The effects of pure CO_2 poisoning, as thus induced, are stated as loss of coördination (ataxia), stupefaction, and loss of consciousness (Haldane). CO_2 is thus a narcotic in large concentrations.

Sodium Lactate.—Whenever the activity of skeletal muscle outstrips the recovery oxidation the muscles "go into debt for oxygen," a process that involves out-pouring of sodium lactate into the blood (page 87), and in consequence the appearance of lactates in urine (page 91). Only a small part of the lactate produced escapes through the kidneys; most of that given off into the blood dialyzes back again, in part into the general tissues, and in part, after the exercise is over, into the muscles from which it came. It is supposed to be reconverted into glycogen (page 88). It appears that there is a fairly close relation between the amount given off in urine and the total quantity formed in the body. Some out-pouring of lactate presumably occurs in any case of anoxemia (page 221), and not exclusively in the anoxemia of vigorous muscular activity. To what extent the symptoms which attend severe anoxemia (page 222) may be due to the accumulation of sodium lactate cannot be stated. It is probably not a major factor in their causation. Many observers have suggested that *feelings of fatigue or weariness* (page 736), which must have their immediate seat in nervous tissues, may be caused, at least in part, by sodium lactate acting upon some nervous structures. It is also possible, although not proved, that long exposure to sodium lactate in high concentration may affect the heart unfavorably.

Phosphates and Sulphates.—These appear in urine in the form of salts which are excreted from the circulating blood. Their main sources are obviously those pointed out above (page 231), phosphoric acid from phosphatides and nucleoproteins, sulphuric acid from cysteine. Phosphoric acid is bound up with calcium metabolism, as already shown (page 230). It is not, therefore, wholly a waste product. Sulphuric acid (except in complex combination) is not known to function in man in any other respect than as a waste product. It occurs to a slight extent in combination as an inorganic salt, but for the most part in the form of nitrogen-containing ethereal sulphates, unions of sulphuric acid with compounds formed in the large intestine by putrefaction, and absorbed thence into the blood (page 426). These are looked on as "detoxication" compounds, through whose formation putrefactive products that would otherwise be poisonous are rendered innocuous.

The Ketone Bodies.—In Chapter XI (page 186) a picture of fat metabolism is presented according to which fats are converted to carbohydrates through a series of stages, one of which involves ketone body formation. The primary ketone is aceto-acetic acid, the others are two immediate derivatives, *β-hydroxybutyric acid* and *acetone*. The three compounds are known also as *acetone bodies*. They are present in the blood in important amounts only when exceptional quantities of fat are being metabolized, as in total starvation and in diabetes mellitus (page 180). The ketones con-

stitute "fixed acids" from the standpoint of neutrality regulation (page 165), being eliminated ordinarily through the kidney after union with ammonia (page 148). A certain amount of acetone is said to escape in the expired air, giving rise to the characteristic acetone odor of the breath in diabetes and in starvation. The significance of the acetone bodies as factors in cell environment is chiefly in their tendency to deplete the alkali reserve, and so establish a harmful or even fatal acidosis (page 167).

Cholesterol. -The status of this compound as a metabolite is difficult to fix. It is probably an essential constituent of living protoplasm, as already pointed out (page 37). It is so slightly soluble that only minute concentrations can be carried in the blood. It is much more soluble in normal bile, in which it is constantly present to the amount of about 0.07 to 0.10 per cent. It may conceivably be involved in the protoplasmic wastage which is pictured as a feature of basic metabolism (page 60), but differing from protein, which is the main substance undergoing wastage, in that it is eliminated unchanged, and not after decomposition into simpler metabolites. Cholesterol is of concern clinically because slight disturbances in the normal processes of elimination result in the precipitation of the substance, in union with other débris of the liver, in the form of *gall stones*. In Chapter XII, page 209, the views of some investigators linking cholesterol metabolism with adrenal cortex function are mentioned.

NITROGENOUS METABOLITES.

Ammonia Compounds.—Ammonia compounds occur in minute concentrations in blood, chiefly in the form of carbonate, but other acids unite with ammonia in proportion as they are formed in metabolism or ingested in the food, and so may appear also. In addition to sources in deaminization of amino-acids (page 182), and perhaps in protoplasmic wastage (page 60), there is considerable ammonia formation in the large intestine due to bacterial putrefaction of the intestinal contents. This ammonia is absorbed from the intestine into the blood, passes to the liver, and is there converted into urea (Folin and Denis). The formation of ammonia in the kidneys in the conservation of more valuable bases has already been referred to (page 148). The ammonia from all these sources except the last is almost wholly "detoxicated" by conversion into urea (page 183), only the unconverted residue appearing in the blood. It has been shown (Nash and Benedict) that in connection with the formation of ammonia in the kidneys there is some escape of the same into the venous blood, contributing to the total quantity present therein. The chief path of ammonia excretion is the kidney, about 3 per cent of the nitrogen of normal urine being ammonia

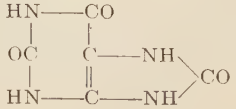
nitrogen. There is also slight excretion in sweat, as evidenced by the ammoniacal odor of the latter.

Ammonia compounds are injurious to protoplasm, although they seem not to be so violently toxic as was held at one time. Their injurious nature is brought out by establishing in experimental animals a so-called Eck fistula, *i. e.*, an artificial union between the portal vein and the inferior vena cava. The effect is to divert the blood which flows through the capillaries of the alimentary tract from its ordinary subsequent course through the liver. Animals so treated develop symptoms of poisoning, particularly on a heavy meat diet, which is the type of diet favorable to intestinal putrefaction. The symptoms are probably due, in part at least, to ammonia. They may be so severe as to lead to a fatal termination. When this experiment was first performed it was interpreted as showing that the deaminization of amino-acids occurs mainly in the intestinal walls in connection with the process of absorption, and that the resulting ammonia is carried in the portal blood direct to the liver to be there "detoxicated." It was only after Folin and Denis had shown the source of portal-blood ammonia to be chiefly from putrefaction in the large intestine, that the present view of the deaminization process (page 182) began to take form.

Urea.—This compound is the most abundant dissolved constituent of urine (page 147). Its concentration normally ranges between 2 and 3.5 per cent, the total daily output on an average diet being 25 to 30 gm. The main source of urea is as a "detoxicated" product of ammonia as pointed out above.

Urea is eliminated in health as fast as formed, and in the low concentrations found in normal blood (22 to 30 mg. per 100 ml.) has no influence on metabolism, so far as known. Disturbances of kidney function may interfere with elimination, in which case the urea content of blood and tissue fluids may rise very high. Two hundred milligrams of urea or more per 100 ml. blood may thus be attained. Various symptoms (headache, dizziness, gastro-intestinal disturbances, coma and death), develop in connection with the presence of high urea concentrations, but it is questionable how far they are attributable to the urea itself, as other nitrogenous metabolites increasing in quantity parallel with the urea are more likely responsible.

The Purin Bodies.—In Chapter II (page 41) the characteristic chemical constituents of cell nuclei are stated to be nucleoproteins, complex substances which yield, on decomposition, a series of so-called *purin bodies* among other things. The most familiar of these is uric acid:



This substance, in the form of monosodium urate, is found in the blood of man and the anthropoid apes as the chief end-product of the metabolism of nucleoproteins, and hence presumably of the chromosomes, assuming nuclear metabolism to involve the chromosomes. In all other mammals yet studied, with a single exception, the metabolism goes a step further and *allantoin* is formed. The single exception is one variety of dog, the Dalmatian coach dog, which differs from other dogs but resembles man in forming uric acid instead of allantoin. The difference is attributable to an enzyme, *uricase,* which catalyzes the conversion of uric acid into allantoin, and is present in the bodies of most mammals, but not in man, apes or the Dalmatian breed of dogs. In birds and reptiles uric acid is synthesized from urea, and becomes, in these forms, the chief end-product of all nitrogenous metabolism, and not solely of that of nucleoproteins. Beside uric acid two closely related compounds, *xanthin* and *hypoxanthin*, are formed in considerably smaller quantities in nuclear metabolism, along with occasional traces of guanine and adenine. These form about 10 per cent of the total output.

Exogenous and Endogenous Purins.—All foodstuffs containing cellular material, which means practically all except milk, eggs, animal and vegetable fats, starch and sugar, including syrups, contain more or less purin substances, which are present on account of the metabolism which prevailed in the cells prior to the use of the material as food. These purins are absorbed from the alimentary tract, along with the nutrients and other food constituents, and so appear in blood and urine. They are referred to as *exogenous purins,* to indicate that their source is outside the body. The only way to avoid their occurrence in blood and urine is to confine the diet to non-purin-containing foodstuffs. When this is done the only purins in blood and urine are of *endogenous origin, i. e.,* formed within the cells, and chiefly, if not wholly, in the course of nuclear metabolism. Concentrations of endogenous urates in normal human blood have been found to range from 0.7 mg. to 3.5 mg. per 100 ml., with an average of 1.8 mg. The daily production is about 0.2 to 0.6 gm. (values expressed as uric acid).

Deposition of Urate Crystals.—There is satisfactory evidence that in certain pathological conditions the concentration of urate in blood may rise to twice the normal or more. The salt is so slightly soluble in blood that increase is apt to be attended by deposition of urate crystals, particularly in the cartilages. In fact, deposition may occur, even though there has been little or no increase in the concentration of urates in the blood. The conditions bringing this about are not well understood. When painful reactions develop in connection with, or as the result of, urate deposition the condition constitutes *gout.* There is no evidence that urates in solution have any influence on metabolism.

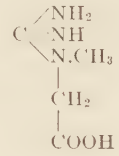
Methyl Purins.—Caffeine, and the related alkaloids, theobromine and theine, are taken commonly in the diet, since they are the peculiar constituents of coffee, tea and cocoa. All three are methyl substitution products of purins, caffeine being tri-methylxanthin. They have definite stimulating effects, particularly on the central nervous system, a fact which accounts primarily for their adoption as articles of diet. They are not animal metabolites, but are included here because of their close relationship to animal purins and because they have a certain importance as factors in cell environment. There is so much individual variation in reaction to these alkaloids that statements of general application are difficult to make. It is a matter of familiar observation that many persons drink coffee and tea daily for many years without appreciable ill effect, while others are clearly the worse for even moderate indulgence. The methyl purins are eliminated through the kidneys, in part unchanged, and in part after splitting off of one or more methyl groups. They appear not to be converted into uric acid. They have a decided diuretic effect (page 440), which may be in part due to changes in the circulation of blood through the kidney (page 356), but is thought to be due also in part to a direct action upon the kidney tubules.

Creatinine and Creatine.—Next to urea the most abundant nitrogenous constituent of urine is *creatinine*. If both creatinine and the closely related compound *creatine* are excluded from the diet the daily elimination in any given individual becomes very uniform, and remains so, apparently indefinitely, during health. There is considerable individual variation, the range for adult males being given as 15 to 32 mg. creatinine per day per kilo body weight; for females, 9 to 26 mg.; for children from infancy to puberty, 9 to 17 mg.; for infants, 6.7 to 10 mg. (Shaffer and others). There is satisfactory evidence that the creatinine is chiefly, although probably not altogether, a waste product of muscle metabolism. The marked uniformity of production would indicate that only basic metabolism is involved, but data presented below (next page) implicate functional metabolism to some extent.

The different levels of creatinine elimination in different individuals can be accounted for as due to the fact that they differ in ratio of muscle mass to body weight. In general the more muscle one has the more creatinine he will eliminate. This is not the whole story, for it is quite possible for "normal" persons to have different levels of basic metabolism in their muscles as well as in other tissues. The suggestion has been offered that the "quality" of individual muscles may be related somehow to the quantity of creatinine produced by them.

The facts about creatinine just stated naturally arouse interest in the metabolic processes behind its formation. Unfortunately, in

spite of the fact that a great deal of study has been devoted to the problem, and much important information brought to light, there is still uncertainty as to which of several conceivable metabolic reaction series may lead to creatinine as a final waste product. The original view, which still is accepted widely, is that the immediate precursor is *creatine*, methyl-guanidine-acetic acid:



This latter compound is readily demonstrable in considerable quantity in skeletal muscle (4 mg. per gram tissue in adults), in smaller proportions in brain and testis, and in minute quantities in most other tissues.

Several observers have sought to assign to creatine a function in connection with muscle tonus, proceeding, however, on the assumption that tonus is a different phenomenon from ordinary contraction. With the accumulation of evidence indicating that tonus in skeletal muscle is nothing more than the normal contraction of a few muscle fibers (page 691), the relation of creatine must be to ordinary contraction if to any processes involving functional metabolism. Actual evidence that appears to connect creatine with contraction is the finding (Schulz) that creatinine elimination invariably rises above the usual level during muscular work, and falls below it immediately thereafter, the fall so nearly balancing the rise that, taking the day as a whole, elimination is practically uniform. If this finding is confirmed, and if creatine proves to be the precursor of creatinine, It will be necessary to revise somewhat our present picture of functional metabolism in skeletal muscle (page 87), so as to show how creatinine relates to it. Attempts to make such a revision in the present state of knowledge are too speculative to be profitable.

Creatine Elimination.—In normal adult males on a creatine-free diet the urine does not contain creatine. It is intermittently present in the urine of women (continuously during pregnancy) and is eliminated regularly by children of both sexes. It appears in the urine of men under special conditions, chief among which are fever, hyperthyroidism, diabetes or other conditions of carbohydrate deficiency, high-protein diet and starvation. In the main, these fall into one or another of two classes; conditions tending toward excess basic metabolism, or conditions involving the mobilization of storage proteins (page 181). It is reasonable to assume that in the first case there is liberation of creatine in greater than normal quantity, or under conditions of disturbed equilibrium, so that the

ability of the cells to hold it is exceeded, giving rise to direct creatine elimination. In mobilization of storage proteins it is likely that there is release of cell creatine as part of the process, some of which escapes from the blood by way of the kidney. The occasional creatine elimination in women, and its constant elimination in children, indicate that the tissues retain their creatine by a narrow margin, which is not attained in childhood, and may be easily overstepped in adult life, more easily in women than in men.

Creatine is probably derived from protein. The amino-acid argenine has a guanidine radical which relates it nearly to creatine. Another possible, but less likely, source is choline, which, as pointed out earlier (page 20), is a constituent of lecithin, the commonest phosphatide. Neither creatine nor creatinine is known to influence metabolism when present in the cell environment as a waste product en route to the kidneys.

Pigments.—For reasons and by means not understood there is normally more or less continuous degeneration of red corpuscles (page 262) with release of their contained hemoglobin into the blood. The hemoglobin is in turn decomposed in such a way as to set the pigment portion free, and this is again decomposed into an iron-bearing and an iron-free residue. The latter is definitely a waste product. Other pigments besides hemoglobin also occur in the body, and appear to be subject also to decomposition, with production of waste substances allied to, if not identical with, the iron-free residue of the blood pigment.

The waste residues of body pigments are eliminated chiefly in the bile; to a much less extent in the urine. Excretion in bile is represented by the bile pigment, *bilirubin*, together with an oxidation product, *biliverdin*, and a reduction product, *urobilin*. The ratio of bilirubin to biliverdin differs in different animals. In general, bilirubin predominates in carnivorous forms, making their bile yellow, while in herbivorous animals biliverdin is in excess, making the bile green. Urobilin is present in normal bile only in small concentration. It is, however, the form in which the major portion of the pigment waste leaves the body, both bilirubin and biliverdin being converted into it by reduction during the passage of the material through the intestine. Small amounts of urobilin and related pigments are given off in the urine. These have been generally supposed to be derived by absorption from the intestine into the blood, and conveyed thence to the kidney, but doubt has recently been cast on the reabsorption of pigments from the intestine (Whipple). This doubt appears to be well founded; in view of it, the source of urinary pigment is to be sought in the cells in which body-pigment decomposition takes place, rather than in the intestine.

It has long been known that the conversion of blood pigment into

bile pigment is carried on by liver cells (both *Kupffer* cells and hepatic epithelium, according to Whipple). Recently other body cells, particularly the vascular endothelium and serous mesothelium, have been shown to possess the same property. Thus the presence of pigment wastes in the blood, and their direct excretion in the urine, can be readily accounted for.

In obstruction of the bile passages (obstructive jaundice) the blood becomes charged with bile. The resulting symptoms, so far as they are caused by bile in the blood, are so slight as to make it doubtful whether the bile pigments, or any other constituents of bile, have any significant influence on cell metabolism.

Summary.

Since soluble metabolites are conveyed in the blood stream to all parts of the body, they are likely to enter the environment of any or all cells. Even though they may be primarily waste products, they must be taken into account as probable factors influencing metabolism.

Insoluble metabolites are laid down in or near the cells which produce them. In general, they constitute the salient portions of supporting and protective structures. They may be inorganic or organic, permanent or susceptible of resorption. In mammals proteins related to gelatin are important organic, and lime salts important inorganic, metabolites of this class.

Soluble *non-nitrogenous* metabolites include carbon dioxide, water, sodium lactate, salts of phosphoric and sulphuric acids, ketone bodies and cholesterol. *Nitrogenous* metabolites include urea, ammonia compounds, purin bodies, creatinine and creatine and pigments of bile and urine.

Carbon dioxide is the most abundant metabolite, and probably the most significant of those that are primarily waste products. It is present in venous blood to the extent of about 50 ml. per 100 ml. blood, partly as $NaHCO_3$, partly in combination with hemoglobin and partly in simple solution as H_2CO_3. During the passage of blood through the pulmonary capillaries CO_2 escapes into the alveolar air, due to the lower CO_2 pressure prevailing there than obtains in the tissue fluids and in the blood itself.

By overventilating the lungs CO_2 can be "blown off" from the blood, with the result that both the H_2CO_3 content and the $NaHCO_3$ content become sensibly reduced. The blood, in consequence of porportionally greater reduction in H_2CO_3, takes on a lower hydrogen-ion concentration. The condition is known as *alkalosis*. The lowered CO_2 content of the blood, called *acapnia*, is attended by characteristic symptoms, including light-headedness, depression of gastro-intestinal activity, impairment of the "relaxing power" of the heart and tetany.

The increased CO_2 production of muscular exercise is ordinarily taken care of by augmentation of the circulation and of lung ventilation, so that the tissues are not exposed to excess CO_2. It is possible experimentally to produce such excess. The result shows CO_2 in large concentration to have a decided narcotic action.

Sodium lactate is poured into the blood whenever the active muscles "go into debt for oxygen." It is likely that anoxemia, from whatever cause, is attended by some out-pouring of lactate. No very positive statements can be made regarding the effects of lactate on the tissues in these cases. Various unfavorable actions, including the causation of feeling of weariness have been attributed to it.

Phosphoric acid appears in blood and urine as a waste product of phosphatide and nucleoprotein metabolism. Sulphuric acid is formed in cysteine decomposition. The latter acid unites with putrefaction products from the large intestine to form ethereal sulphates.

The *ketone bodies,* aceto-acetic acid, β-hydroxybutyric acid and acetone, appear in the blood and urine when fat is metabolized in unduly large amounts. These bodies act as "fixed acids" in relation to neutrality regulation. They tend to deplete the alkali reserve and so to bring on a harmful or in extreme cases a fatal acidosis.

Cholesterol is difficultly soluble in blood plasma, more soluble in bile, in which it is present as an excretory product. It is the characteristic component of gall stones.

Ammonia compounds are formed in deaminization of amino-acids, in protoplasmic wastage (presumably), in the large intestine in the course of putrefaction of intestinal contents and in the kidney as a base-conserving reaction. The ammonia, except from the last source, is almost wholly "detoxicated" by conversion into urea. Only small unconverted residues appear in the blood and urine.

Urea is the most abundant dissolved constituent of urine, representing, as it does, the end-product of ammonia "detoxication." Its concentration in normal urine ranges between 2 and 3.5 per per cent; in normal blood between 22 and 30 mg. per 100 ml. In disturbed kidney function its concentration in blood may rise as high as 200 mg. per 100 ml. It is doubtful whether even in such high concentrations urea has significant influence on metabolism.

The *purin bodies* are end-products of nuclear metabolism chiefly. They occur in human blood as the monosodium salt of uric acid (90 per cent), xanthine and hypoxanthine, guanine and adenine (10 per cent). In all mammals so far as known, except in man, apes and Dalmatian coach dogs, the enzyme *uricase* is present and carries the metabolism a step farther, with formation of *allantoin.* Birds and reptiles form uric acid as the chief end-product of all nitrogenous metabolism.

Uric acid of *endogenous origin* is in blood in concentrations of

0.7 to 3 mg. per 100 ml. The daily production is 0.2 to 0.6 gm. Urate crystals may be deposited in certain tissues, notably in cartilage, in connection with relatively slight increases in urate concentration in the blood. Methyl purins, caffeine, theobromine and theine, formed in plant metabolism, are common substances of human consumption. They are taken on account of their stimulating action. They have also a definite diuretic effect.

Creatinine is thought to be chiefly if not wholly the end-product of a distinctive metabolism of skeletal muscles in which the closely related compound *creatine* is also involved. The production of creatinine within the body is very uniform from day to day, and bears close relation to the mass of skeletal muscle present.

Creatine is not eliminated in adult males except under bodily conditions apparently involving excess basic metabolism or the mobilization of storage proteins. It occurs constantly in the blood and urine of normal children and intermittently in women. Neither creatine nor creatinine is known to influence metabolism while present in blood as a waste product.

The waste residues of hemoglobin and other body pigments are eliminated chiefly as the bile pigments, *bilirubin*, *biliverdin* and *urobilin* (the last in small concentration in bile). During their passage through the intestine the first two are converted by reduction into the last, which represent, therefore, the main form in which pigment wastes are expelled from the body. The decomposition of body pigments occurs largely but not exclusively in the liver. Vascular endothelium and serous mesothelium share in the process. The urobilin and other pigments which appear in urine are thought to be derived from the latter source.

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PART III.

BODILY MAINTENANCE.

CHAPTER XV.

THE MAINTENANCE OF CELL ENVIRONMENT IN VERTEBRATES.

Metabolism Depends on and is Influenced by Cell Environment.—In the chapters preceding this an attempt has been made to picture the various types of metabolism of which living cells are capable, and to outline various environmental factors that appear to be significant in the metabolic processes. Two general characteristics of metabolism have been stressed: (1) That it is fundamentally automatic and self-sustaining, going on indefinitely, so far as we know, if certain environmental conditions are fulfilled; (2) that it is subject to alterations both in nature and amount in response to particular changes in the environment. Different environmental factors have obviously different values in respect to both these characteristics of metabolism. Oxygen, for example, is essential to the metabolism of most kinds of cells, but provided enough is present, and an injurious excess is avoided (page 225), does not appear to influence either the nature or the amount of metabolic activity. Adrenin, on the other hand, is perhaps not essential to the life of any cell yet may play an important part in regulating the metabolism of a great many.

The Problem of Maintenance in Vertebrates.—The problem that confronts an organism like a vertebrate, composed of hundreds of millions of cells, each carrying on its characteristic metabolism, is that of providing every cell with as much as it requires of each substance that contributes to metabolism, ridding each one of accumulating wastes and excess heat, as fast as formed, and controlling the factors that influence metabolism so that each cell or cell group shall live, grow and function in proper balance with all the others. The complexity of this last phase is evident when we realize that the activity of one cell group is likely to affect the metabolic processes going on in many others. This is invariably true both of nervous and of hormone-producing tissues (page 197)

it is likely to be true of others as well, since all produce and give off metabolites of one kind or another (page 46).

Immediate Cell Environment Restricted in Amount.—The situation is further complicated by the fact that the immediate cell environment, which is composed of tissue fluid, has perhaps not more than about one-tenth the volume, in mammals, of the tissues whose needs must be supplied by interchanges with it (page 158). The cells must satisfy their metabolic requirements by primary interchanges with a medium present in too small amount to be able by itself to meet the pressing metabolic needs of the cells for more than a few seconds (page 215) and the less pressing for only a comparatively brief period.

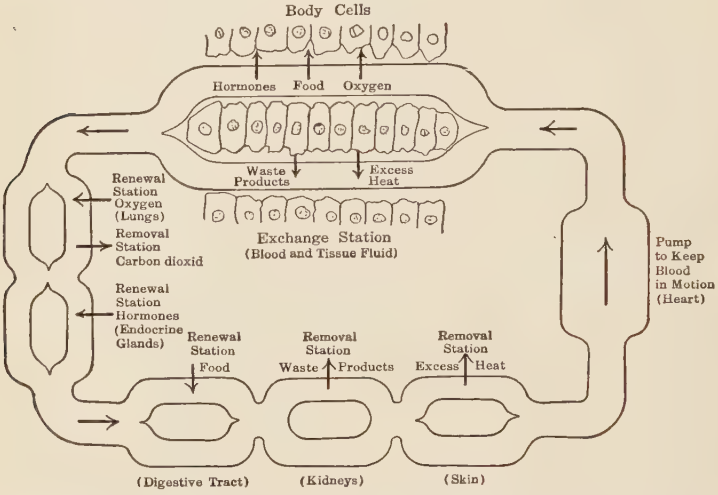

FIG. 26.—Diagram to illustrate how suitable cell environment is maintained by the flow of blood through a series of capillaries. (Martin's Human Body, Henry Holt & Co., Publishers.)

Circulating Blood Extends the Environment.—The difficulty is met by confining a portion of the body fluid within a system of vessels and moving this confined fluid, familiar to everyone as *blood*, in a fairly rapid stream past the regions occupied by cells. In the cellular regions the moving blood comes into interchange relationship with the nearly stationary tissue fluid, through the thin walls of the capillaries. These walls permit both dialysis and filtration, under limitations discussed in another place (page 37). Thus as fast as the cells withdraw oxygen or other needed materials from the tissue fluid immediately surrounding them, the loss is made good by dialysis or filtration from the blood. Carbon dioxide and other metabolites, and the large amount of heat evolved in active metabolism, are taken up by the blood, again through dialysis, or in

the case of heat by dissemination. These processes can go on indefinitely because fresh blood is constantly replacing that with which exchanges have been made.

Renewal of Blood.—Since the volume of circulating blood is itself restricted, the arrangement implies a further provision by which the blood, after once passing through the tissue capillaries and giving off or taking up whatever it may, is in turn renewed before returning to perform the same function again. This further mechanism consists of several additional sets of capillaries, through which the blood circulates, and in which it comes into exchange relationships exactly opposite in each case to those obtaining in the tissues. Thus in the pulmonary capillaries the diffusion gradient for oxygen is from alveolar air to blood and the gradient for carbon dioxide from blood to alveolar air (page 364); in the capillaries of the intestinal tract the gradient for salts, nutrients and vitamins is from the lumen of the intestine into the blood or lymph (page 420); in each endocrine gland the gradient for its specific hormone is from gland cells to blood (page 149); in the excretory organs the movement of metabolites is from blood to ducts (page 143); in the skin the gradient for heat dissipation is from blood to the exterior (page 446). The situation is illustrated diagrammatically in Fig. 26.

BODILY MAINTENANCE.

The problem of maintenance thus transfers itself from the environment of individual cells to the structures and actions by which the blood is kept in motion from one set of capillaries to another, and by which, in the areas in which renewal of blood is to take place, the proper conditions for renewal are fulfilled. Each set of structures, including accessories of one kind and another, makes up what has long been known as a *physiological system*. The systems devoted especially to maintenance are the *circulatory*, by which the blood is passed from set to set of capillaries; the *respiratory*, in which the blood is renewed in respect to oxygen and carbon dioxide; the *digestive*, in which it is renewed in respect to inorganic salts, nutrients and vitamins; the *endocrine gland* system, in which there is renewal in respect to hormones; the *excretory*, in which there is elimination of wastes; the *temperature-regulating system*, in which dissipation of heat occurs.

Control of Maintenance Systems.—The present section is devoted to these systems as they function in man. For purposes of presentation it is obviously necessary to deal with them individually. An important point, however, to be kept constantly in mind, is that they do not function independently. Each one is subject to a control that obliges it to carry on its activities in a manner suited to the requirements of the body as a whole, and hence varying as

bodily requirements change. It is in this control that the operation of the body as a unified organism, rather than as a colony of living cells, chiefly manifests itself. The mechanism of control is partly through the nervous system (on the efferent side the autonomic system chiefly, page 128), and partly through the action of hormones, as indicated in Chapter XII, page 197. Details of the control in each system are given in connection with the description of its action.

(The *endocrine gland* system is coördinate in importance with the other systems listed above. It is not, however, discussed in this section under a separate chapter heading because the main facts so far as they apply to the hormones affecting general metabolism have already been presented (Chapter XII), and the various hormones having highly restricted functions are described in connection with the systems with which their functions are allied.)

The Mechanisms of External Adjustment Supplement Those of Maintenance.—For bodily maintenance, as a whole, still other mechanisms are called into play, *i. e.*, those concerned with adjustments of the organism to the external world. The mechanisms are the skeletal muscles, the sense organs and the main part of the nervous system. A section to follow concerns itself with them in detail. In the present connection only one point is to be stressed concerning them, namely, that they have an active role in supplementing the systems immediately devoted to maintenance. To illustrate: The digestive system begins its special function with the introduction of food into the mouth. But both the securing and the ingestion of food usually involve several senses, as well as various muscular movements, controlled and accurately coördinated by the nervous system. The regulation of temperature is another process in which, particularly in man, the functioning of the definitive temperature-regulating mechanism must often be supplemented by such actions as building fires or putting on warm clothing. In this interaction of the mechanisms of adjustment with those of maintenance we have further emphasis on the nature of the organism as an entity, to be studied and interpreted as such, even though our methods of approach compel us often to deal intensively with individual tissues, organs or systems.

Summary.

The maintenance of metabolism in vertebrates involves the provision for each of the many cells in the body of adequate quantities of materials contributing to metabolism, the removal from each of its accumulating wastes and the regulation of metabolism in different parts, so that all shall function in harmony, in accordance with the needs of the body as a whole.

The immediate cell environment, *i. e.*, tissue fluid, is too restricted

in amount to serve, except momentarily, either as a source of utilizable material or as a depository for waste.

The effective cell environment is extended through the circulation of blood. Continuous interchanges between cells and tissue fluid are possible because there are concurrent interchanges between tissue fluid and blood.

The blood is renewed, in turn, by passing through capillary areas in which interchanges take place, opposite in direction to those which occur between blood and tissue fluid.

Bodily maintenance depends directly on the effective functioning of the various capillary areas (with their accessory structures) in which renewal of blood takes place. Each of these constitutes a *physiological system*. The systems concerned primarily with maintenance are *circulatory, digestive, endocrine, excretory* and *temperature-regulating*.

The maintenance systems are subject to control, partly through the nervous system and partly through the action of hormones. The control operates to cause each to function in accordance with the requirements of the body as a whole.

The mechanisms of external adjustment: sense organs, skeletal muscles, and the main part of the nervous system supplement the maintenance systems in various ways to be outlined later.

CHAPTER XVI.

BLOOD: PLASMA AND CORPUSCLES.

BLOOD PLASMA.

The liquid portion of blood as it circulates in the bloodvessels is known as *plasma*. This is a colorless and viscous liquid of specific gravity about 1.030, as contrasted with about 1.055 for whole blood. The difference is due to the red corpuscles, which have specific gravity of about 1.090. Plasma consists of water carrying in solution larger or smaller quantities of every soluble substance that is taken into the body or that is produced within it in metabolism. These various constituents can be classified, although not rigidly, into two groups: (*a*) Materials that form part of the specific composition of blood; (*b*) materials in transit from one set of capillaries to another. Group *b* has been discussed more or less fully in the preceding section. Our present interest is with Group *a*. This group includes a series of substances that are, so far as we can judge, essential to the functioning of blood as a vehicle for the transportation of the materials which compose Group *b*, and also substances that serve the body as a whole by defending it against the inroads of disease-producing microörganisms.

Inorganic Salts.—First to be considered are sodium chloride and other simple salts. The general significance of salts as constituents of living protoplasm and of the cell environment has been previously discussed (pages 24, 172). So far as the salts pass out from the blood into the tissue fluids and cells in connection with these functions they fall into Group *b*. While in the blood stream, however, sodium chloride particularly, and the other salts in proportion, must be looked upon as essential constituents of blood because they are the chief factors in determining its osmotic pressure. It is obvious that blood will always tend to come into osmotic equilibrium with the tissue fluids, and through these fluids with the cells, subject to the modifying influence of the Donnan equilibrium (page 32). The type of protoplasm of which the human body is composed is so organized that its osmotic pressure cannot depart widely from that of an $\frac{M}{8}$ NaCl solution (about 0.73 per cent) without injury or even destruction. Preservation of the integrity of the cells clearly requires, therefore, that the tissue fluid and blood shall maintain virtually the same osmotic pressure.

All the soluble constituents of blood contribute to its total osmotic pressure. Sodium chloride, which is present in approximately $\frac{M}{10}$ concentration, is, however, the most significant in this respect, accounting by itself for about 60 per cent of the whole osmotic pressure.

The red corpuscles of the blood (page 261) are also in osmotic equilibrium with the plasma, and their integrity depends on the maintenance of normal osmotic pressure in the latter. In fact the primary reason (although not the only one) why pure water cannot be safely injected into the veins in case of hemorrhage, and why $\frac{M}{8}$ NaCl or Ringer's solution must be used if any watery injection is to be made, is that pure water would lower the osmotic pressure of the plasma below that of the red corpuscles; there would be movement of water into the latter (page 31) which would swell, and if the change in osmotic pressure were great enough would burst, releasing the hemoglobin to go into solution in the plasma. The profound changes in oxygen transport, as well as in osmotic pressure and blood viscosity, that would result have already been pointed out (page 216). In mammals they are too great to be borne. Consequently complete disruption of corpuscles is fatal.

Plasma Proteins.—About 7 to 8 per cent of human blood plasma, by weight, consists of characteristic proteins that are looked upon as specific blood constituents rather than as nutritive materials in transit. There is no evidence that the tissues can draw on the blood proteins for nutriment; on the other hand, they are so constant in amount and so characteristic in composition as to suggest strongly a definite role in the functioning of blood itself.

The plasma proteins fall into two main physico-chemical groups on the basis of their solubility in distilled water. About two-thirds the total quantity present is soluble, and classifies as *serum albumin;* the remainder is insoluble in pure water, although soluble in dilute salt solution; this constitutes the group of *serum globulins* (protein solubilities are relative rather than absolute; page 22). The classification based on solubility is useful in the laboratory and to some extent for purposes of description. Its theoretical significance is imperfectly understood. Both serum albumin and serum globulin are mixtures of two or more chemically distinct proteins, but whether these chemical differences are important or not is not known, except in the case of one of the globulins, *fibrinogen* (see next paragraph). The presence in blood of inorganic salts, and the fact that its hydrogen-ion concentration is near neutrality, imply the aggregation of the proteins into micellæ showing the Donnan equilibrium (page 21); in other words, a colloidal structure.

For the most part the function of the plasma proteins appears to

be physical or physico-chemical rather than strictly chemical. They exert a moderate buffer action (page 164), impart to the blood a necessary degree of viscosity (page 351) and are thought by their colloidal osmotic action to play an important part in holding blood volume fairly constant (page 271). The one plasma protein known to be important chemically is *fibrinogen*, which has a role in blood-clotting (page 273). This protein is present in only small concentration, constituting about one-seventh of the whole amount of globulin, or about 0.4 per cent of the weight of plasma.

If an animal is bled, and the blood replaced, as fast as drawn, by a suspension of red corpuscles in Ringer's fluid, the concentration of plasma proteins can be materially reduced without a fatal result. As the animal recuperates there is a restoration of plasma protein, rapid at first and then more gradual, requiring five to seven days for completion. The liver is involved in some way in the restoration process, as shown by the fact that when the liver is impaired, as in phosphorus or chloroform poisoning, the regeneration of plasma proteins is much slower than when the liver is normal. In the case of fibrinogen the evidence indicates not only that the liver is mainly concerned, but also that maintenance of an adequate fibrinogen concentration in blood depends on continuous fibrinogen formation. In both phosphorus and chloroform poisoning the fibrinogen content of blood falls off, to zero if the poisoning is extreme, and the power of the blood to clot is correspondingly lessened.

IMMUNIZING AGENCIES.

For a number of years it has been known that the mechanism by which the body prevents or overcomes infectious disease consists in part of chemical agencies present in the blood. These are grouped under the general head of *immunizing agencies*, and their action constitutes *humoral immunity, i. e.*, immunity effected by the blood plasma. In the study of these agencies, a study that has been carried on extensively, some of the most significant, and at the same time least understood, facts in the biology of the higher animals have been brought to light. A brief outline of the most salient of these, together with some of the conclusions that have been drawn from them, are all that can be given here.

Antigens and Antibodies.—Two facts in particular stand out as basic to the entire picture. The first of these is that if any naturally occurring water-soluble protein is introduced into the blood of one of the higher animals to which it is foreign, *i. e.*, differing from the animal's own proteins, it stimulates the cells of the latter's body to produce a substance to which the name *antibody* is assigned (amboceptor in Ehrlich's terminology). Some investigators believe all

cells to have the property of forming antibodies. Others think it more probably confined to the blood-forming and reticulo-endothelial (macrophage) tissues (page 258). The antibodies are known only by their action; as yet no one of them has been obtained in pure state, at least not in sufficient quantity to admit of chemical study. For this reason we cannot say certainly whether antibodies are definite chemical compounds or not. They occur in blood always in some sort of relation to the serum globulin, but there is good evidence that they are not simply modified globulin; some investigators even doubt that they are proteins. There is no doubt that they are colloidal. Any agency that stimulates the cells to the production of antibodies is called an *antigen*. The evidence indicates clearly that only large molecules in colloidal state can act as antigens. It has been widely held that only proteins have the property, but recent evidence is contrary to this view (Eberson).

The second basic fact of immunity is that any given antibody has the power of reacting with the particular kind of antigen that stimulates cells to produce it, and, so far as we know, with no other. Each particular antigen appears to stimulate the cells in a specific manner, leading to the production of an antibody that is also specific. An astonishing thing about this relationship is that the special nature of the cell producing the antibody does not appear to affect the product. Any cell in any animal that has the property of forming antibodies will react to the stimulus of a given antigen by forming an antibody that behaves exactly like the antibody produced by any other cell of any other animal under the same stimulus.

The Immunization Process.—The blood of most higher animals, including man, can be shown to contain various antibodies that appear to be present normally. Reference is made to some interesting examples in later paragraphs (page 279). *Artificial immunity* is established by introducing an *antigen-containing* medium into the tissues or, what amounts to the same thing, into the blood of the animal in which antibodies are to be developed. The minimum effective amount of antigen is extraordinarily small. It is stated that as little as 0.000000005 gm. of egg albumen introduced into a guinea-pig will cause the production of antibodies in demonstrable quantities. No chemical tests yet devised, and only the most refined physical tests, will reveal the presence of protein in such dilution as this. The laws governing the relationship between the amount of antigen introduced and the amount of antibody formed have not yet been worked out. In some cases small doses of antigen appear more effective than larger doses. Long exposure to the action of antigen, on the other hand, ordinarily results in a larger output than does brief exposure. The common practice in experimental immunization is to give three injections of antigen-containing

material at intervals of three days. In bacterial infection the antigens are present, of course, so long as the bacteria continue to flourish. There is a so-called "incubation period" for antibody formation. In most warm-blooded animals it is six to ten days. This may be interpreted as the time required for the cells to alter their metabolism under the influence of antigen so that they produce and pour out antibodies into the blood. The change in metabolism outlasts the presence of the antigen, so that antibodies continue to be poured out after the antigen has been neutralized or otherwise disposed of. The persistence of the effect is variable; some immunities last throughout life; others disappear in a few days, perhaps in extreme cases in a few hours. Individual antibodies may last as much as thirty days, as is proved by injecting antibody-containing blood into the veins of a non-immune animal, which thereupon may become immune for about that period (passive immunization). If several antigens are introduced together the corresponding antibodies are all produced simultaneously, and so far as we know, by all antibody-forming cells. What the limit to this action may be appears not to have been determined.

Results of Immunization.—(*a*) *Precipitation and Agglutination.* An animal that is immune is so because it has antibodies circulating in its blood. The immunity applies only to the particular kinds of antigens for which these antibodies are specific. In other words, if any such antigens enter the blood of an immune animal they are at once acted upon by their appropriate antibodies. The reaction will occur when the mixture is made in test-tubes as well as when the antigen is injected into the vessels of the immune animal. The effect of the reaction depends on the form in which the antigen is introduced. The simplest case in actual practice is when the antigen is in the form of a soluble protein. Reference to pages 25 and 28 will recall the fact that at the hydrogen-ion concentration of the body, which is near neutrality, and so at some distance from the isoelectric points of the common proteins, the latter cannot exist in simple solution, but on account of the molecular and electrical stresses present are bound to aggregate into micellæ showing the Donnan equilibrium. It is upon such micellæ that the antibodies exert their action in the case under consideration. Of the various suggestions that have been offered to account for this action, the simplest are that it is either a lowering of the electrical potential which the Donnan equilibrium sets up and which is the chief factor in keeping the micellæ apart (page 28), or an increase in the attractive force exerted by the surface molecules, making the attraction greater than the repulsive force of the like electric charges on the micellæ. Whether for one of these, or some other cause, the result is a clumping together of the micellæ into larger aggregates, usually going on to complete precipitation. This is the *precipitation reac-*

tion in immunity, and the antigen that sets it off is called a *precipitin*. A noteworthy feature of the precipitation reaction is that it throws down as part of the precipitate a large fraction of the serum globulin present in the blood, although this serum globulin has nothing to do, as far as we know, with the primary reaction, which is between antibodies present in the blood and the proper antigen introduced from outside. The involvement of the serum globulin may be interpreted as due to the disturbance in colloidal equilibrium which the antibody-antigen reaction brings about.

Bacteria and red blood corpuscles contain proteins which may function as antigens in producing immunity, and also in setting off the antibody-antigen reaction. Both actions can be obtained by introducing intact bacteria or red corpuscles as well as by introducing isolated proteins obtained from them. When the antibody-antigen reaction is evoked by means of intact cells there is a clumping together of the cells known as *agglutination*. It is generally believed that the mechanism is the same as is operative in the precipitin reaction. A practical significance of the agglutination of red corpuscles is given in a later paragraph (page 280).

(*b*) *Antitoxin Action.*—Certain bacteria, notably those of diphtheria and tetanus, produce and pour out into their environment soluble poisons called *toxins*, which have the capacity to act as antigens. It is not certain that the antigen action of bacterial toxins is due to their contained proteins, since they may be freed of all protein, as far as chemical tests show, without losing their antigenic property. The antibodies produced by the tissue cells under the stimulus of toxins are called *antitoxins*. Antitoxins neutralize the poisonous properties of their specific toxins by some sort of direct combination. The combination does not destroy either the toxin or the antitoxin; it merely renders the toxin innocuous. This can be proved by a treatment which separates the toxin-antitoxin combination into its constituent parts, when the toxin resumes its poisonous character. Antitoxins are like the antibodies that cause precipitation and agglutination in that they are specific for the toxins that stimulate to their production, and also in that a given antitoxin produced by the cells of an animal of one species is exactly the same in action, and presumably also in nature, as that produced by the cells of an animal of a different species. It is this latter fact that makes possible the utilization of immune horse serum as a source of diphtheria antitoxin for use in human disease. There is considerable evidence, too technical for presentation here, indicating antitoxins to be substances of different character from other antibodies. In the main features of their action, however, they agree closely, as already shown.

(*c*) *Cytolysis.*—Bacteria and other living cells, as well as red blood corpuscles, have been stated just above to contain antigens

and so to be capable both of stimulating antibody formation and of setting off the antigen antibody reaction. The agglutination which may thus be brought about has already been described. We have now to note an additional effect that may be seen when antigen-containing cells are brought into contact with blood that has in it specific antibodies. The effect is typical for most kinds of cells, although some are known that resist it. The action is a disintegration of the cells. It is referred to as a *lytic* reaction. If bacteria are disintegrated the action is *bacteriolysis;* if red corpuscles, *hemolysis;* if cells in general, *cytolysis.* The specific agents are referred to as *bacteriolysins, hemolysins* and *cytolysins* respectively. A very interesting fact about the lytic reactions is that the actual cell disintegration is not caused by the action of the antibody on the antigen-containing cells, but by a third agent, the *complement* (*alexin* in Bordet's terminology), normally present in all bloods. *Complements* have destructive power for cells but cannot exercise it until after the cells have reacted with their specific antibodies. The evidence for the existence and action of complements is based on the fact that they are readily destroyed by heating the blood to 55° C. for a few minutes. If cells are added to a blood that is immune against them, but in which the complements have been destroyed by heat, no lysis occurs. The lytic action can be restored, however, by adding any unheated blood, showing that the complements are the same in all bloods, at least in all mammals that have been studied. The same fact shows that the complements are nonspecific. One cell is disintegrated as readily as another provided the specific antibody is present, and provided the cell is of a sort susceptible to complement action. The evidence is fairly clear that the complement is colloidal. It is quite conceivable that complement action depends wholly on a particular colloidal organization of the blood proteins, in which case the complement is not to be thought of as a definite chemical compound.

(*d*) *Anaphylaxis.*—All the immunization phenomena thus far considered depend on the presence of antibodies in the circulating blood and on reactions that take place in the blood stream. It has already been noted that all these can be caused to take place experimentally in test-tubes. We turn now to a phenomenon in which antibodies and antigens are concerned, but in which the cells are involved rather than the circulating blood. This phenomenon, known as *anaphylaxis,* occurs under very special conditions, and is thought by some investigators to depend on the formation of special antibodies, different in action, and presumably in constitution also, from those to which the effects described above are due. Not all species of animals nor all individuals within susceptible species form these special antibodies. The condition for their formation in the cells of a susceptible organism is the introduction

of an antigen in a single small dose. This restriction is essential to success; administering precisely the same antigen to the same organism by the usual technique of repeated larger doses (page 253) results in typical immunization as described above.

The process of special antibody formation, which is the essence of anaphylaxis, is known as *sensitization*. After it has taken place in any susceptible organism administration of the specific antigen is followed by the expected antibody-antigen reaction, but in this case apparently in the tissue cells instead of in the blood stream. The result is a sudden and violent disturbance in cellular metabolism. The ensuing manifestations are often startling, and in some species nearly always fatal. They make up the symptom-complex known as *anaphylactic shock*. A noteworthy fact is that the shock symptoms, while different in different species, are the same in a given species regardless of the nature of the antigen and its specific antibody.

The cells may participate more or less generally in the metabolic disturbance that constitutes anaphylactic shock, but the manifest symptoms consist chiefly of spasmodic contractions of smooth muscles. The differences seen in different species appear to depend largely on the localization of the spasms in different smooth muscle groups. For example, in guinea-pigs and in human asthmatics spasms of the bronchial musculature produce the conspicuous, and in guinea-pigs usually fatal, effects; in dogs the splanchnic area is chiefly involved; in rabbits the pulmonary bloodvessels, and by indirection the right heart, are chiefly affected. Only a comparatively small percentage of human beings appear to be susceptible to anaphylaxis; these are likely to develop hay fever or asthma, or to be sensitized by single doses of diphtheria antitoxin.

There is as yet no final decision as to whether antibody production is a function of all cells in the higher animals or only of certain groups (page 253). It appears, however, that whenever the organism contains antibodies they are present in most if not all the body cells, having either originated within them or migrated into them from the blood.

A view of anaphylaxis widely held is that the phenomenon is due to insufficient production of antibodies of ordinary "immunization" type, so that not enough are present in the blood stream to combine with all the antigen introduced, and so to protect the tissue cells against metabolic disturbances which invariably result from the occurrence of antibody-antigen reactions within them. Evidence offered by Manwaring against this view is: *(a)* That an animal *sensitized* toward a given antigen can have its blood replaced by transfusion (page 279) with blood from another animal of the same species *immunized* against the same antigen, and hence well charged with antibodies, yet when the usual dose of antigen is administered

the animal develops anaphylactic shock; (*b*) a normal dog can be sensitized passively by replacing its blood with blood from an *anaphylactic* donor, but not with blood from an *immune* donor, although the same antigen may have been responsible for the antibody production in both cases. If shock were due simply to insufficient antibodies in the blood stream it would be difficult to explain these experiments which seem to show clearly that the antibodies responsible for anaphylactic shock are not identical with those to which immunization is due.

BLOOD CELLS.

Modern histologic investigation has established the important fact that the blood corpuscles, both red and white (the *erythrocytes* and *nucleated blood cells*), form part of a great cell system closely related embryologically to ordinary endothelium, and including beside the blood cells proper, an array of widely distributed cells of fairly definite character found scattered among the fibroblasts, in the serous membranes, in the lymph nodes, the bone-marrow, the spleen, the wall of the intestine and in the liver as "Kupffer" cells. The cells making up this array are known by various names. The terms *histiocyte* (Kiyono) and *clasmatocyte* (Ranvier) are frequently used. They are also often called *reticulo-endothelial* cells and, in common with certain blood cells (page 260), *macrophages*.

Nucleated Blood Cells.—Examination of a drop of human blood under the microscope reveals the presence among the very numerous red corpuscles of several sorts of nucleated cells. The total number of the latter, lumping all kinds together, is usually around 5000 to 7000 per cubic millimeter. Any marked increase above the normal number constitutes a *leukocytosis;* a marked decrease is a *leukopenia*. Both conditions are of much clinical significance. Their further discussion falls outside the scope of the present work.

From the standpoint of the physiologist, the most satisfactory of the many classifications of nucleated blood cells that have been proposed is one which recognizes three main types: *Leukocytes proper* (granulocytes, polymorphonuclear cells, neutrophiles, basophiles and eosinophiles), *monocytes* (large mononuclear cells) and *lymphocytes* (smaller non-phagocytic mononuclear cells). The attempt to assign specific functions to each of these classes of cells is beset with great difficulty, yet fairly definite ideas seem to be crystallizing out of the great mass of experimental data that has accumulated.

The *leukocytes proper* are now generally accepted as being primarily *phagocytes* (scavenger cells), *i. e.*, endowed with the property of engulfing minute particles by amœboid action. In the body the particles taken up by leukocytes are chiefly bacteria. When a

localized area of the body becomes infected the infecting organism, or the tissues under their influence, apparently give off some chemical substance which acts by *chemotaxis* (page 116) to cause leukocytes to migrate to the spot in large numbers, and upon arrival there to engulf the bacteria. In the opinion of some investigators (Wells), both the chemotaxis and the engulfing action depend mainly, if not wholly, on an effect of the chemical substance to lower the surface tension of the leukocytes on the side on which the attracting substance is most concentrated.

The phagocytic action of leukocytes is manifested almost wholly toward bacteria. On the theory held by Metchnikoff, to whom the conception of phagocytic action is mainly due, that this restriction is a matter of size of particle, they are commonly designated as *microphages*, to distinguish them from cells that engulf larger particles, and are accordingly called *macrophages* (see below).

As a matter of fact, the essential feature of the phagocytosis of bacteria by leukocytes is not the simple act of engulfing, but the destruction of the engulfed bacteria, in a manner suggesting enzyme action, by bactericidal substances (endolysins) present within the leukocytes. Furthermore, leukocytes will systematically engulf and destroy only such bacteria as contain specific antigens for antibodies already present in the blood and them only after the antibody-antigen reaction has occurred. The antibodies that thus underlie leukocyte function are known as *opsonins*. It is probable, but not absolutely certain, that they are exactly the same antibodies as interact with complement in the plasma bacteriolysis described above (page 256). In fact, the bactericidal action of phagocytes resembles closely that of complement. In both cases the antibody must react with the antigen-containing cell before lysis can occur. In phagocytosis the active lytic agent is inside the leukocytes; in plasma bacteriolysis it is in solution in the blood.

Another function suggested for the leukocytes, and for which there is considerable experimental support, is that they take part in the transport of fat from inside the epithelial cells that line the intestine, across the inner cell membranes of these cells, to the lacteal fluid (page 413). Great numbers of leukocytes are normally present in the intestinal villi, particularly during absorption, and they are typically well charged with fat. It is still an open question, however, whether normal fat transport actually depends to any extent on leukocyte action.

Leukocytes proper ordinarily make up 60 to 75 per cent of the total number of nucleated blood cells. The average number of leukocytes per cubic millimeter is thus between 3000 and 5000. In the healthy adult the only site of formation of these cells is stated to be in the *hematopoietic* (blood-forming) tissue in the red marrow of the bones. The process is that of proliferation of antecedent

cells, known as *myelocytes*. Production usually keeps even pace with disintegration, so that the number circulating in the blood is about uniform. However, there is a large reserve constantly present in the bone-marrow which may, on proper stimulation, be poured into the blood stream, rapidly raising the count.

A subclass of leukocytes, the *eosinophiles*, are noteworthy in that, while they are present only in small numbers in normal blood, they are abundant in cases of infection with various animal parasites, and in the neighborhood of many kinds of tumors. A second subclass, the *basophiles*, distinguished by their reaction to basic dyes, are markedly increased whenever the bone-marrow shows signs of augmented activity. Beyond this fact, there is little specific information about them.

The second group of nucleated blood cells are the *monocytes*. These share with the reticulo-endothelial cells (page 258) the property of being strongly phagocytic for particles of various sorts that may find their way into the blood, as well as for cell detritus generally. The designation *macrophage* is properly applied either to a freely wandering monocyte or a stationary reticulo-endothelial cell. There is general agreement that the monocytes are essentially reticulo-endothelial cells that have freed themselves from attachment, although there is no evidence that a monocyte once freed ever reattaches itself, and difference of opinion as to whether the ability of reticulo-endothelial cells to wander free is widely distributed or confined to a few localities.

Monocytes make up about 6 per cent of the total number of nucleated blood cells, giving a count of around 300 to 400 per cubic millimeter of blood.

Their macrophage action is generally stated to be less effective than that of the stationary reticulo-endothelial cells. The basis for the statement is the observation that when foreign particles are introduced into the blood they are rapidly withdrawn, subsequent examination showing them to have been taken up in enormous numbers by the reticulo-endothelial cells. In connection with wound repair, however, the monocytes have an important function in clearing away cell débris.

Monocytes are also of great importance in the adult as providers of trephones for proliferating fibroblasts and epithelial cells (page 64). They share this property with the lymphocytes (see below), but apparently not with leukocytes proper, which seem to be devoid of it.

Lymphocytes make up about 20 per cent of the number of nucleated cells, giving a count around 1000 to 1500 per cubic millimeter. They are formed in lymphoid tissue and set free primarily in the lymph, finding their way into the blood *via* the lymphatic channels. Their antecedent cells appear to be closely related to

the myelocytes that give rise to leukocytes in the bone-marrow (page 260). Lymphocytes are rapidly formed. In fact more enter the blood every twenty-four hours than are present in it at any one time. This implies an active escape of lymphocytes from the blood. They pass in enormous numbers out onto mucous surfaces, particularly in the intestine. What function they serve here is not fully established. Suggestions are that they aid in digestion, and also that they defend the organism against bacterial invasion. That they mediate this function in tuberculosis is very clearly shown. They must do it by chemical means, since they are not phagocytic. In common with the monocytes, they produce trephones and so promote nutrition of epithelial cells and fibroblasts.

Red corpuscles (erythrocytes), biconcave disks about 0.0088 mm. (8.8 μ) in diameter, are present in blood to the number of about 5,000,000 per cubic millimeter in healthy adult males (4,500,000 in females). In sheer bulk they loom large, constituting between 40 and 50 per cent the total blood volume.

Each corpuscle consists of a *stroma* composed of the same substances as are basic for living protoplasm, *i. e.*, proteins, phosphatides, cholesterol and inorganic salts, heavily charged with *hemoglobin* (90 to 95 per cent of the total weight). The stroma is ordinarily pictured as forming a spongy mesh work in whose interstices the hemoglobin is held. As a matter of fact, the precise physicochemical relationship between hemoglobin and stroma is not yet known. The osmotic reactions of the corpuscles are like those of sacs inclosed in semipermeable membranes. The corpuscles either take up or discharge water, according as the surrounding medium is hypotonic or hypertonic (page 32). Fat solvents cause disintegration of the stroma with discharge of the hemoglobin, presumably by their action on the phosphatides.

A characteristic of the stroma is its ready distortion under pressure, which makes possible the passage of corpuscles through capillaries too narrow to receive them otherwise. Release of pressure is followed promptly by elastic return of the corpuscles to their normal shape.

Origin and Fate of Red Corpuscles.—Red corpuscles as found normally in human blood are not nucleated, nor do they give positive evidence of containing any living protoplasm. The test of life, *i. e.*, basic metabolism (page 59), gives practically negative results when applied to human blood (page 218). The corpuscles are derived from antecedent living cells, known as *erythroblasts*, which in adults are apparently localized in the blood-forming (hematopoietic) tissues of the bone-marrow. As the erythroblasts proliferate they form cells which either synthesize or take up hemoglobin and then extrude the nucleus, thus assuming the adult condition. Normally the process is completed before the corpuscles enter the blood

stream, but in case of regeneration after hemorrhage, or other conditions which stimulate to specially active corpuscle formation, nucleated corpuscles are commonly found in the blood. The production of erythrocytes is continuous and rapid. A fairly conservative estimate is that something like 1,000,000,000 are normally produced and given off into the blood every minute.

This rapid formation just balances an equally rapid destruction. A reasonable assumption, for which there is no absolute proof, is that the corpuscles gradually deteriorate as they move about the circulation, so that in the course of ten to thirty days (most estimates fall within these limits) they become subject to disintegration. A view for which there is considerable evidence is that the red cells become broken up into fragments while still circulating (Rous and Robertson). The fragments are then acted on, mainly by reticuloendothelial cells in the liver, spleen and elsewhere in the body (page 258). The net result is the conversion of the non-ferrous residue of the blood pigment into bile pigment (page 240), and the conservation of the iron and other utilizable materials for further use. It is suggested, but not yet proved, that the same cells that have to do with the conversion of waste blood pigment into bile pigment are also concerned in the synthesis of hemoglobin for deposition in the newly forming erythrocytes (Whipple).

After hemorrhage the production of red corpuscles is somewhat more rapid than their destruction, so that after several days or weeks, depending on the severity of the hemorrhage, the normal count is regained.

Hemoglobin Content.—The various functions of red corpuscles are described elsewhere (pages 164, 215). In the main they hinge about the hemoglobin. It follows that the blood cannot be considered normal unless it contains the proper amount of hemoglobin. The average hemoglobin content of normal blood is given as 14 gm. per 100 gm. blood, or about 0.028 mg. per 1,000,000 corpuscles. The oxygen-carrying capacity of the blood is obviously a function of the total amount of hemoglobin present in it. This amount may vary either by a change in the number of corpuscles present or by an alteration in the hemoglobin content of individual corpuscles. In general the former change is more likely to occur, at least in civilized man, than the latter. If there is a serious decrease in hemoglobin content, from either cause, the condition is known as *anemia*. If there is a pronounced increase in number of corpuscles (overloading of individual corpuscles with hemoglobin is not known to occur) the condition is *polycythemia*. For purposes of comparison the normal hemoglobin content is called 100 per cent, and degrees of anemia expressed in percentage of normal. Instruments for estimating hemoglobin content are based on color comparisons, either whole blood or a carefully diluted sample being compared

with a standard color scale calibrated in percentages. Determinations of polycythemia are based on corpuscle counts rather than on hemoglobin determinations. It is obvious that corpuscle counts may also be used as indices of anemia in such cases as show diminution in number of corpuscles without accompanying decrease in amount of hemoglobin per corpuscle.

BLOOD PLATELETS.

These minute structures occur in blood to the number of about 300,000 per cubic millimeter. They are looked upon as cytoplasmic fragments of certain cells (*megacaryocytes*) in the bone-marrow. The only function known for them is in connection with the act of blood clotting (page 274). They break up quickly when blood is shed unless special precautions are observed. For this reason they escaped discovery until after the middle of the last century.

BLOOD AS A PHYSICO-CHEMICAL SYSTEM.

The blood has been discussed earlier in respect to its function as a buffer system (page 164), as a carrier of oxygen (page 215) and as a carrier of carbon dioxide (page 232). L. J. Henderson and associates have established the important fact that the various factors concerned in the performance of these functions are so interrelated that changes in any one are necessarily accompanied by changes in all the others. In other words, a physico-chemical equilibrium exists among the various factors, and whenever the equilibrium is disturbed by a change in any one it is readjusted automatically by accompanying changes in all the others. Examples of readjustments in individual factors have been given in earlier chapters; the "dissociation curve" of oxyhemoglobin (page 216) is one; the difference in CO_2 content between arterial and venous blood (page 232) is another.

L. J. Henderson and co-workers direct attention to seven variables whose equilibrium relationships are particularly significant for the functioning of blood as a buffer and as a carrier of respiratory gases. These are: *Uncombined oxygen* (symbolized in Fig. 27 by O_2 and measured as oxygen tension in mm. Hg.); *total oxygen* (symbolized by HbO_2 and measured as percentage saturation of hemoglobin, page 216); *uncombined carbon dioxide* (symbolized by CO_2 tension and measured as CO_2 tension in mm. Hg.); *total carbon dioxide* (symbolized by total CO_2 and measured as volume CO_2, including that present as bicarbonate, per 100 ml. blood); *hydrogen-ion concentration of the plasma* (symbolized by pH_s and expressed as pH); *volume of red corpuscles* (symbolized by Vol. and expressed as percentage of corpuscle volume, the latter being considered unity when equal to 40 per cent of the total blood volume); finally, the

ratio of the concentration of anions within and without the corpuscles (symbolized by *r*). The significance of Vol. (corpuscle volume) is as an index of the partition of water between plasma and corpuscles as affected by osmotic factors and by the Donnan equilibrium. The

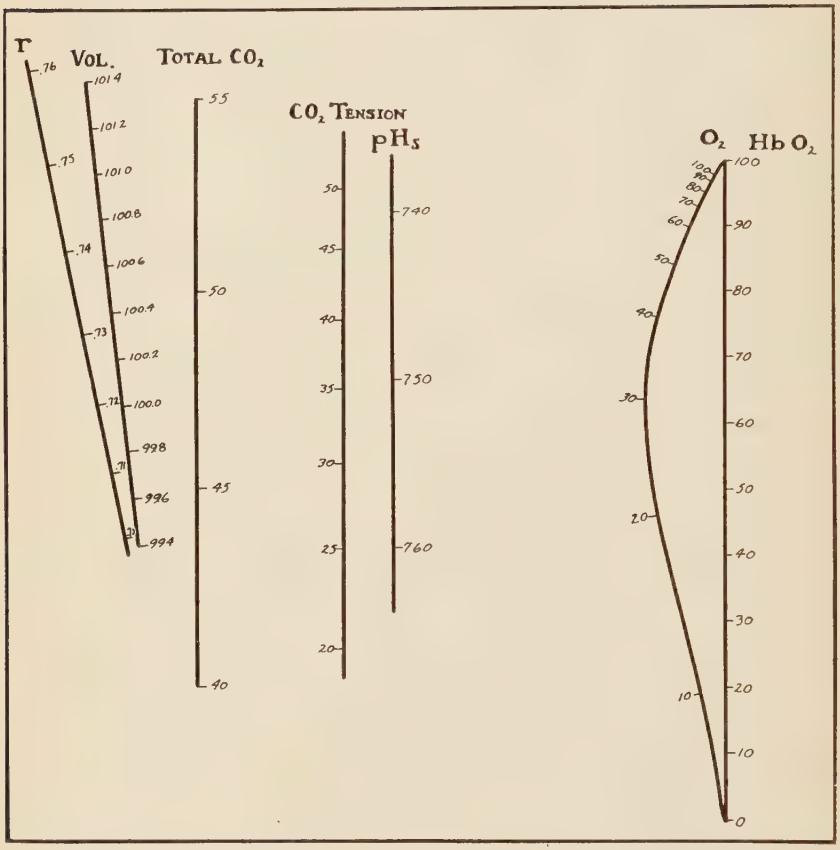

Fig. 27.—Nomogram by which the values of various physico-chemical variables in blood are readily determined provided any two are known. O_2, uncombined oxygen; HbO_2, percentage saturation of hemoglobin with oxygen; CO_2 tension, uncombined carbon dioxide; total CO_2, total carbon dioxide, including that present as bicarbonate, per 100 ml. blood; pH_S, hydrogen-ion concentration of plasma; Vol., volume of red corpuscles (considered as unity when equal to 40 per cent total blood volume); *r*, ratio of anion concentration within and without the corpuscles. (L. J. Henderson and co-workers.)

significance of *r* (anion ratio) is chiefly as an index of the distribution of chlorides between plasma and corpuscles, and relates to the uptake of HCl by the latter (page 164).

By means of a chart called a *nomogram* (Fig. 27) the value of each factor at any given equilibrium within the range of conditions

occurring in blood can be readily determined. A straight line so drawn across the chart as to cut all seven lines gives at its points of intersection the values of the seven variables for that particular equilibrium. In practice one must know the values of two factors in order to establish the locus of the equilibrium line. If in a sample of arterial blood, for example, the value of HbO_2 is found to be 96 and of total CO_2 48, completing the construction shows the CO_2 tension to be approximately 42 mm., the O_2 tension about 80 mm. and the plasma pH about 7.44. This method of charting physico-chemical equilibria is susceptible of considerable extension and wide application and promises to be of great assistance in the solution of physiological problems.

Summary.

Blood plasma, the watery part of blood, carries in solution portions of every soluble substance that is taken into the body or that is produced within it in metabolism. The constituents of plasma form two groups: (*a*) Specific components; (*b*) materials in transit.

Inorganic salts are present in blood as materials in transit, but they also function as specific components. In the latter capacity they serve to maintain the osmotic pressure of the blood at a level suitable both for the body cells and the red blood corpuscles. Sodium chloride which is present in $\frac{M}{10}$ concentration is largely concerned in this action.

Plasma proteins constitute 7 to 8 per cent by weight of human blood plasma. About two-thirds is *serum albumin;* the remainder is *serum globulin*. These designations are based on solubility differences. There are two or more chemically distinct proteins in each group. The plasma proteins are colloidal, *i. e.*, aggregated into micellæ showing the Donnan equilibrium.

The known functions of the plasma proteins are to exert a moderate buffer action, to impart necessary viscosity, and to exert an osmotic influence that tends to hold blood volume constant. One of the globulins, *fibrinogen*, has a role in blood-clotting.

The plasma proteins are formed by body cells. Cells of the liver are known to have an active part in the process. In the case of fibrinogen the liver is the essential organ. Blood loses the power to clot when the liver suffers extreme damage.

Immunizing agencies are important constituents of plasma. They are a large factor in the body's defense against infectious disease.

Foreign water-soluble proteins function as *antigens* in stimulating the blood-forming and reticulo-endothelial tissues, and perhaps other tissues as well, to the production and out-pouring of specific *antibodies*. The chemical nature of antibodies is unknown. They

are colloidal, and are specific in that they will react with the particular sort of antigens that stimulate to their production, and with no others. Antibodies produced by one species are identical in action with those produced by any other species, provided the antigen is the same.

Antibodies appear to be to some extent normal constituents of blood. Particular kinds can be caused to be formed artificially by introducing media containing appropriate antigens into the tissues or blood. The minimum effective dose of antigen is extraordinarily small. Long exposure to antigen action leads to the production of larger amounts of antibody than does brief exposure. The incubation period is six to ten days. After antibody formation is started it persists for a time which is different for different antibodies, ranging from a lifetime to a few hours.

In the *precipitation* reaction antigen (precipitin) is introduced in soluble form into a blood immune to it and the effect of the reaction is to cause a clumping together and precipitation of the colloidal micellæ. In this action the serum globulin becomes involved and is largely precipitated.

The *agglutination* reaction is seen when the antigen (*agglutinin*) is introduced as a constituent of organized structures like bacteria or red blood corpuscles. The antigen-containing objects clump together (agglutinate) as a resul of the antigen-antibody reaction.

When the antigen is a bacterial *toxin* the corresponding antibody is an *antitoxin*. The action is a neutralization of the poisonous property of the toxin without altering irretrievably either the toxin or the antitoxin.

Normal blood contains *complements*, which have the property of causing cell disintegration (*cytolysis*) in antigen-containing cells that have reacted with their specific antibodies. Not all kinds of cells are susceptible to this action.

When single small doses of antigen are administered to susceptible organisms special antibodies, presumably differing from those described above, are produced. An organism in which this occurs is *sensitized* toward the specific antigen. Whenever the latter is administered to an organism so sensitized a violent disturbance of metabolism ensues. This special phenomenon of immunity is *anaphylaxis*. The bodily manifestations, which are due chiefly to smooth muscle spasms, constitute *anaphylactic shock*.

The blood cells, *erythrocytes* and *nucleated cells*, form part of a great cell system, closely related to endothelium and fibroblasts, and including the widely distributed *reticulo-endothelial* cells, present in specially large numbers in liver and spleen.

Nucleated blood cells are present in numbers of 5000 to 7000 per cubic millimeter in normal blood. Marked increase constitutes *leukocytosis;* marked decrease, *leukopenia*. Nucleated blood cells

are classified in this book as *leukocytes proper*, *monocytes* and *lymphocytes*.

Leukocytes proper, known also as *microphages*, have a definitely phagocytic property in respect to bacteria. This action includes both the engulfing and the destruction of the bacteria. Its systematic occurrence depends on the presence in the leukocytes of non-specific *endolysins*, and in the blood of antibodies (*opsonins*) specific for the antigens present in the bacteria to be attacked.

Leukocytes are also assigned by some investigators the function of taking part in the transport of fat from the cells that line the intestine to the lacteal fluid.

A subclass of leukocytes, the *eosinophiles*, show increase in number in cases of infection with animal parasites and also in the neighborhood of tumors. The site of leukocyte formation is stated to be in the blood-forming (*hematopoietic*) tissue in the red marrow. Leukocytes are derived by proliferation of antecedent *myelocytes*.

Monocytes, together with reticulo-endothelial cells, are designated as *macrophages*, because of their phagocytic action toward foreign particles that may enter the blood and toward cell detritus. Monocytes are thought to be essentially reticulo-endothelial cells that have wandered free. They share with the lymphocytes the property of synthesizing trephones, and so may nourish proliferating fibroblasts and epithelial cells.

Lymphocytes are formed in lymphoid tissue by proliferation of antecedent cells that appear closely related to myelocytes. They are formed rapidly and disappear rapidly, chiefly by migration out unto mucous surfaces. They have been supposed to aid digestion; they apparently defend the organism, but not by phagocytosis, against bacterial invasion, especially in tuberculosis. They also produce trephones in common with monocytes.

Red corpuscles (*erythrocytes*) give a count of about 5,000,000 per cubic millimeter in adult males (4,500,000 in females). The corpuscle consists of a *stroma* and *hemoglobin;* the latter forms 90 to 95 per cent of the dry weight. The stroma is yielding and elastic in texture. It functions osmotically like a semipermeable sac enclosing the hemoglobin.

Red corpuscles, not nucleated normally and apparently not alive, are derived from antecedent *erythroblasts* localized in the adult in the blood-forming tissue of the bone-marrow. The formation, which is rapid, just keeps pace normally with the destruction. The factors regulating corpuscle destruction are unknown. The first step appears to be fragmentation in the blood stream, followed by a decomposing action on the part of reticulo-endothelial and probably other cells, by which the non-ferrous pigment residue is converted to bile pigment and the remainder of the corpuscle, including the iron, conserved.

The average hemoglobin content of human blood is 14 gm. per 100 gm. blood. A value much below normal constitutes *anemia*. It may be due either to a deficiency in number of corpuscles or to a decrease in amount of hemoglobin per corpuscle. Hemoglobin content above the average is due to increase in the number of corpuscles (*polycythemia*).

Blood platelets are present to the number of about 300,000 per cubic millimeter of blood. They are thought to be derived from megacaryocytes by fragmentation. They have a function in connection with blood clotting.

Considered in its aspects as a buffer and carrier of respiratory gases, blood is a *physico-chemical system*, so constituted that changes in any one variable factor are accompanied by changes in all the others, thus readjusting the equilibrium automatically to a new basis. A chart (*nomogram*) permits the values of the various factors to be determined readily at any given equilibrium, provided at least two are known.

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CHAPTER XVII.

BLOOD: QUANTITY, CLOTTING, TRANSFUSION.

QUANTITY OF BLOOD.

Determination by Direct Method.—It is desirable, both for theoretical reasons and for practical purposes, to know how much blood there is in the normal body. Unfortunately, this has proved to be so difficult to determine accurately that the best and most often quoted figures are not beyond question. A method applicable to the lower animals rather than to man is the *direct method*, usually known as Welcker's method. This consists of bleeding the animal as completely as possible, washing out with water the blood that remains in the vessels after bleeding stops, and correcting for the amount of water added. The shortcomings of this method are: (1) Even prolonged washing does not get all the blood, some stagnating in remote small vessels; (2) during the bleeding and washing-out tissue fluid adds itself to the blood in unknown amount, thus introducing an error in the opposite direction. In an attempt to avoid both these errors, some investigators have determined the amount of hemoglobin in a unit amount of blood at the beginning of bleeding, and then macerated the whole animal and determined its total hemoglobin content, calculating blood volume from the data thus obtained. In addition to certain technical difficulties which make this procedure unsatisfactory, there is an inherent source of error in that most of the tissues contain small percentages of hemoglobin-like compounds, that will appear in the analyses and so impair the calculation. On the whole the results obtained by the direct method can be considered only approximately accurate. Average figures are: For dogs (84 determinations), 7 per cent of the body weight; for rabbits (126 determinations), 5.1 per cent body weight. In the fifties of the last century two sets of observers (Lehmann and Weber, and Bischoff) applied the direct method to executed criminals. Bischoff's figures (2 determinations) give an average for man of 7.7 per cent of the body weight.

Determination by Indirect Methods.—Indirect methods of estimating blood quantity have been extensively used on man as well as other mammals. The principle on which they all depend is that of introducing into the circulation a known volume of some accurately detectable substance and, after allowing time for thorough

mixing to occur, determining the amount of introduced substance per unit quantity of blood. Total quantity is then readily computed. The great practical difficulty in this method is the discovery of a harmless, easily titratable substance, that will all stay in the blood stream until thorough mixing has taken place. It is obvious that if the determination is made too soon, *i. e.*, before the blood has passed around the circulation often enough to insure complete mixing, either more or less blood will be indicated than is actually present, according as the blood sample obtained happens to be undercharged or overcharged with the dye. Furthermore, if any of the substance escapes into the tissue spaces while waiting for mixing to occur the determination will indicate more blood than is present.

The search for a test substance that is both accurately detectable in blood and certain to stay in it long enough for the requirements of the experiment has until recently been only moderately successful. The choice has narrowed practically to two sorts, carbon monoxide and non-injurious dyestuffs of the type exemplified by "vital red." The carbon monoxide method (Grehant; Haldane and Smith) depends on the fact that carbon monoxide reacts with hemoglobin to form carbon-monoxide hemoglobin at the expense of an equivalent amount of oxyhemoglobin (page 222). A known quantity of CO is inhaled, and the amount taken up by the blood determined by subtracting the amount subsequently exhaled. The HbCO content of a unit amount of blood is then determined directly, thus all the data are afforded for estimating total blood quantity.

In the dyestuff method a known amount of dye is introduced directly into the blood stream and, after time is allowed for mixing, a known volume of blood is withdrawn and titrated for dye content. The method of titration requires the plasma to be separated from the corpuscles; consequently, the dye selected, vital red, must be one that is not taken up by the corpuscles within the time of the experiment. Furthermore, only plasma quantity is given; the proportion of plasma to corpuscles must be determined separately. The total quantity of dye injected being known, and the amount in each milliliter of plasma after thorough mixing, dividing the first figure by the second gives the plasma volume. Lindhard has recently shown that the blood in the cutaneous veins (from which test samples must be taken) does not become thoroughly mixed with the general blood stream unless the subject moves arms and legs during the five-minute period allowed for mixing. A fixed routine of movements is accordingly prescribed. The average total blood volume of 11 healthy adult males tested by Lindhard was about 5 per cent of the body weight. Since this figure agrees closely with the best determinations of Haldane and Smith by the carbon monoxide method, it is probably a satisfactory average

figure. It implies for a 70-kg. man the possession of about 3.5 liters of blood.

Regulation of Blood Volume.—Studies of blood volume indicate clearly that in health the volume tends to be fairly constant (apparent changes are due to changes in the blood content of the spleen; this organ has the property of varying widely in blood capacity). The volume depends so largely on the amount of water present that the tendency toward uniform volume may be taken to signify that the entry of water into the bloodvessels balances the escape of the same from them. Thus, the factors regulating blood volume are those that determine the movement of water into and out of the vessels. Water can enter the vessels either from the tissue spaces and cells (page 158) or from the alimentary tract. It can escape from the vessels into the tissue spaces and cells; it can be eliminated from the body by the kidneys, sweat glands and other channels of elimination; in case of hemorrhage it can be lost wherever the rupture happens to be located.

Leaving hemorrhage out of account, the forces known to operate in causing liquid to pass out of the bloodvessels are osmotic pressure and filtration pressure. Osmotic pressure will come into play whenever from any cause the blood in the capillaries is more dilute than the surrounding tissue fluid. Filtration pressure is simply the excess hydrostatic pressure of the blood in the capillaries (page 286) over the back pressure of the fluid in the tissue spaces or in the ducts. Its effectiveness in causing liquid to filter out depends in part on the filtration permeability of the capillary walls and in part on the viscosity of the liquid to be filtered through. The more permeable the capillaries the more liquid will tend to escape under a given filtration pressure, but the more viscous the liquid the less will a given pressure force through. The blood owes its viscosity to its colloids, which are predominantly proteins (page 251). These are looked upon as important factors in maintaining blood volume by preventing excessive escape by filtration. It has been shown that salt solution or Ringer's fluid injected into the bloodvessels, as is often done in case of hemorrhage, filters out into the tissue spaces and through the capsular membranes of the kidneys (page 144), too rapidly to be of much service in maintaining blood volume. Better results have been obtained by adding a viscous material like gum acacia to the salt solution. In the condition of *traumatic shock* (page 350) the capillaries are apparently more permeable than normal, and so a feature of shock is the tendency for liquid to escape to an excessive degree from the blood into the tissue spaces, lowering the blood volume materially.

The only well-understood force that causes liquid to *enter* the bloodvessels is osmotic pressure. The escape of water through any of the channels of elimination, kidneys, sweat glands and lungs

(page 159), tends to make the blood more concentrated and so to raise its osmotic pressure above that of the tissue and cell fluids. The resulting movement of water into the blood tends to make these fluids more concentrated in turn. This sets up reactions leading to the intake of water by the organism (page 159). The water thus ingested lowers the osmotic pressure of the intestinal contents, favoring the uptake of water by the blood as it passes through the capillaries of the intestinal tract. From this dilute blood osmosis of water back to the tissue spaces occurs, thus restoring the balance. Since the blood colloids do not escape from the vessels, and since they exert a small but definite osmotic influence, they are looked upon as important stabilizing factors, acting to prevent rapid or extreme fluctuations in blood volume.

During hemorrhage, and afterward, if it is not fatal, there is rapid movement of fluid from the cells and tissue spaces into the bloodvessels. A few hours suffice to restore the former blood volume, provided the loss of red corpuscles has not been so great as to subject the tissues to marked anoxemia (page 221). The force which causes this flow of liquid into the blood is not understood.

Distribution of Blood in the Body.—Closely related to the problem of the total quantity of blood is that of the way in which it is distributed among the various organs and tissues. The fact has already been stressed (page 219) that active tissues obtain increased amounts of oxygen (and by implication of other materials) needed for their augmented metabolism primarily by an increase of the blood flow through them. In part, this increase is due to a speeding up of the circulation as a whole, but in part to a diversion of blood into the active tissues at the expense of others that are less active (page 349). In order to form an idea of the extent to which this diversion can take place, and of the relative degree to which different regions can share in it, it is necessary to know something about the normal quantities present in the various regions.

To an unfortunately great extent it is necessary to rely on estimates; direct determinations obviously cannot be made on man during life, and it is well known that the distribution of blood in the dead body is not the same as in the living. The figures usually cited are a series obtained by Ranke for the rabbit. These are expressed for the different organs in percentages of the whole amount in the body and can be translated into definite quantities only if the total amount of blood in the body is known. Their applicability to man is dubious at the best. In the accompanying table estimates for man assembled from various sources are given. They are expressed in terms of a total blood mass of 3500 gm. (5 per cent of the weight of a 70-kg. man). No high degree of accuracy is claimed, although the figures are believed to give some indication as to how the blood is distributed in the resting body.

ESTIMATED DISTRIBUTION OF BLOOD IN MAN (WEIGHT, 70 KG.).

(*a*)	Not subject to diversion:	
	In heart and large bloodvessels	900 ml.
	In pulmonary circuit	500 "
	In vessels of brain	75 "
(*b*)	Subject to diversion:	
	In vessels of skeletal muscles	850 "
	In vessels of abdominal and pelvic areas	600 "
	Elsewhere in body (skin, bones, etc.)	575 "
	Total	3500 ml.

The above table brings out the important point that more than one-third of all the blood in the body (subdivision *a* of the table) cannot be drawn upon to provide for increased requirements of active tissues. In effect the regions that can experience either depletion or augmentation of blood content are the skin, the skeletal muscles and the abdominal organs (subdivision *b* of the table). The significance of this fact is considered in detail in Chapter XXI, page 347.

BLOOD CLOTTING.

Whenever the walls of a bloodvessels are ruptured, permitting blood to escape, the remarkable property of the blood to clot comes into play. The act of clotting is fundamentally a precipitation of the soluble fibrinogen of the plasma in the form of a dense meshwork of needles of insoluble *fibrin*. The needles are so minute that their characteristic form can be made out only with the aid of the ultramicroscope. Following formation the fibrin needles shrink and draw together, squeezing out the liquid that was caught in the interstices of the meshwork as it formed, but holding the corpuscles firmly. The squeezed-out liquid is known as *serum*. It is essentially plasma minus its fibrinogen, and plus one or more soluble substances formed in or taken up by the blood during the clotting process. The combination of fibrin and corpuscles makes up the characteristic blood clot. In its early stages the clot is of jelly-like consistency, and very sticky, so that it clings to the tissue at the point of hemorrhage, and will presently plug the opening and stop the bleeding, provided the force with which the blood is flowing is not so great as to wash away the clot as fast as it forms.

The salient characteristics of the clotting process are: (1) The precipitation of the fibrin as a meshwork of needles to form the basis of an effective clot, an action stated to be quite different from the ordinary flocculation of a colloid; (2) the setting in train of this process whenever there is rupture of a bloodvessel; (3) the complete absence of clotting so long as the blood is confined within the vessels, and the walls of the latter remain intact. It may be noted that the last feature, namely, the absence of clotting so long as the circulation is intact, is as essential to bodily preservation as the

automatic formation of a clot whenever a vessel suffers rupture. The formation of a blood clot (*thrombus*) within the vessels is always occasion for anxiety, because of the danger of the clotted material being carried along the circulation to a lodgment in some small vessel and blocking the circulation to some important or even vital structure. To have thrombi form on slight provocation would constitute about as great a hazard as to have small injuries develop into fatal hemorrhages.

Clotting Time a Function of Blood CO_2 Content.—The mechanism by which the three characteristics of the clotting process outlined above are maintained is highly complex and not fully understood. Evidence indicating that it is involved in the physico-chemical equilibrium prevailing in blood (page 263) has recently been obtained (Baumberger), the significant finding being that at a given total CO_2 content, about 30 per cent by volume, clotting occurs with maximal speed, the time becoming progressively longer as the CO_2 percentage is raised. At the normal CO_2 percentage of human blood in the bloodvessels, *i. e.*, about 50 (page 232), blood has, therefore, less tendency to clot than after shedding, when by exposure to the air some of its CO_2 escapes. The relation of this finding to other known facts about the clotting process, described below, remains to be determined.

Clotting Time Hastened by Contact of Blood with Tissues.—A fact of both practical and theoretical importance is that the process of clotting is much hastened by the contact of the blood with any of the tissues of the body, except those to which blood is regularly exposed, *i. e.*, the endothelial linings of the bloodvessels and the reticulo-endothelial cells (page 258). In hemorrhage due to any ordinary injury the blood necessarily flows over tissues extraneous to it, and so comes under the influence of this hastening effect. In man and in most mammals the time of clotting under this condition is three to ten minutes at ordinary temperatures. If, on the other hand, the blood is withdrawn directly from a vein by means of clean instruments, and with care to avoid all contact with tissues, one-half hour or more will usually elapse before clotting occurs. In birds and fishes blood thus drawn will usually fail to clot at all.

Details of Clotting Process.—The precipitation of fibrin from plasma in characteristic needle form is due to a reaction between the soluble fibrinogen of the blood plasma and a protein known as *thrombin*, not present, except possibly in traces, in circulating blood, but formed out of a precursor that is normally present. The latter, known as *prothrombin*, *thrombogen* or *proserozyme*, is identified by Cekada as a pseudoglobulin; it occurs both in solution in blood plasma and within the platelets. It is thought by the investigator just cited to be a molecular complex of two thrombins,

one soluble, the other insoluble and both inactive so long as they are united in the precursor. In the presence of calcium the prothrombin is disintegrated into the two thrombins, one of which precipitates out, carrying fibrin down with it; the other remains in solution, except as it, too, reacts with fibrinogen to form fibrin. Thrombin is not formed normally in appreciable amounts in the circulation, notwithstanding the fact that both prothrombin and calcium occur there abundantly. This circumstance argues that there is an agency of some kind operating to prevent the action of calcium on prothrombin, so long as the circulation is intact, but not effective in case of hemorrhage.

Howell has demonstrated the existence of such an agent in the form of a substance to which he assigns the name *heparin*. It occurs in the circulating blood in small concentrations and in the liver abundantly. The compound in apparently pure state can be prepared from extracts of this organ. Heparin contains nitrogen, but neither phosphorus nor sulphur; it is not a protein. The liver can be stimulated to pour it out in quantity into the blood stream by injecting peptone intravenously. So long as heparin is present in the blood calcium is ineffective in decomposing prothrombin into its constituent thrombins, and so the blood will not clot. An essential first stage in clotting is thus the nullification of the action of the small quantity of heparin normally present. The substance which acts as nullifier is a phosphatide, *cephalin*, present in all the tissues, except the endothelial and reticulo-endothelial with which blood is constantly in contact, and also present in the platelets, to be set free whenever they disintegrate. Whenever shed blood comes into contact with tissues the cephalin present in the latter acts to set the prothrombin free from the restraining influence of the heparin, the prothrombin then reacts with calcium and the clotting proceeds. According to Howell's view, this is all there is to the action of cephalin. Both Morawitz and Bordet maintain that cephalin plays, in addition, an active role in the formation of thrombin. Bordet, in particular, looks upon thrombin as a compound of proserozyme (prothrombin), cytozyme (cephalin) and calcium. The blood platelets are rich in cephalin (according to Howell's observations, in prothrombin also). They disintegrate rapidly when blood is shed, unless the blood is prevented from coming into contact with any surfaces which it wets (page 278). The disintegration of the platelets sets free cephalin which neutralizes the heparin and permits the prothrombin to react with calcium to yield thrombin. If the blood flows over tissues an additional amount of cephalin becomes available for the purpose, and the formation of thrombin is correspondingly augmented. In the view of Bordet and of Morawitz the cephalin also enters into the composition of thrombin.

Antithrombin.—It has long been known that the salivary glands of leeches contain a substance (*hirudin*) which will prevent blood from clotting. Recently it has been shown that a small quantity of a hirudin-like substance occurs normally in human blood. This

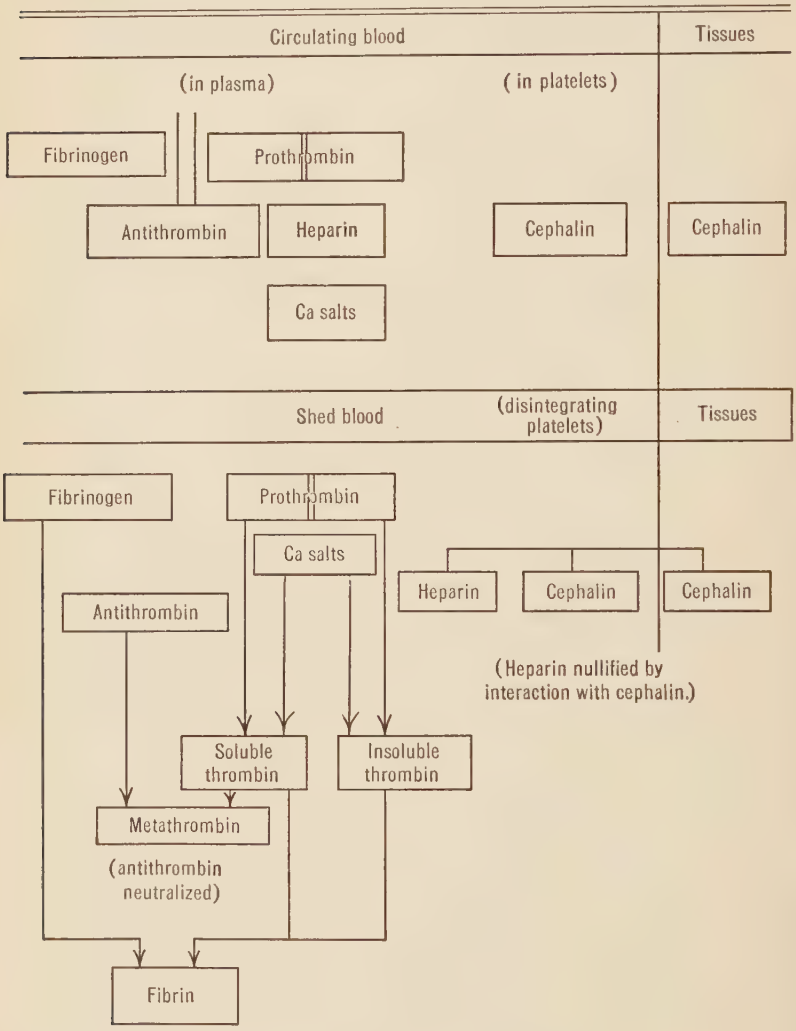

Diagram A.

substance is known as *antithrombin*. It has the property of combining with thrombin to form a compound known as *metathrombin*. Any thrombin thus acted upon is made unavailable for reacting with fibrinogen to form fibrin. Hence, whenever antithrombin is

in excess no clotting can occur. The quantity normally present in blood is sufficient to neutralize such small quantities of thrombin as are likely to be formed as the result of the chance breakdown of platelets within the circulation, and so to prevent thrombus formation ordinarily. There is not enough, however, to interfere effectively with clotting when large scale production of thrombin occurs, as in hemorrhage. Howell has shown that the antithrombin in blood is a derivative of heparin. Its exact nature remains to be determined.

Clot Diagrams.—A convenient method of summarizing various views as to the mechanism of blood clotting by thrombin action is by means of diagrams. The first corresponds in the main with the conception of Howell, as modified by Cekada. The second diagram illustrates the views of Bordet. (The actions of heparin and antithrombin are not considered. The conversion of prothrombin to thrombin is looked upon as involving two stages.)

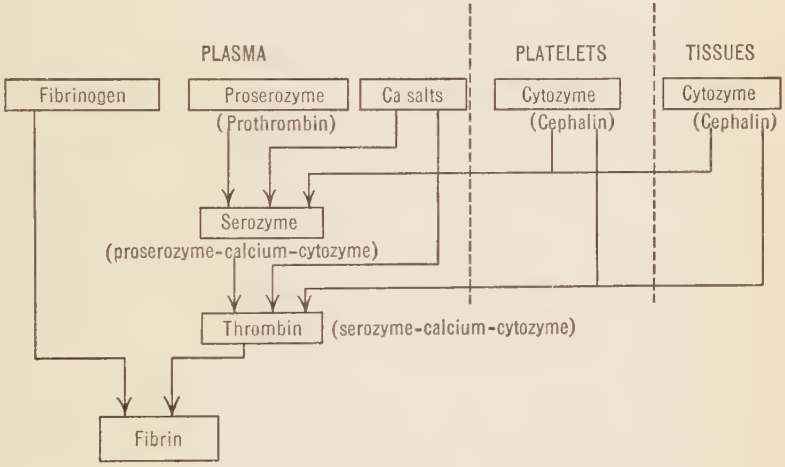

Diagram B.

Defibrinated Blood.—If freshly shed blood is whipped or shaken with any sort of a beater to which the sticky fibrin will cling as it forms, and if the whipping is continued during the ten minutes or so ordinarily required for clotting to be complete, all the fibrin collects on the beater, leaving the blood permanently fluid. Such blood is said to be *defibrinated*. It differs from ordinary blood in that the liquid portion is *serum* (page 273), and not plasma. The fibrinogen has ordinarily all been precipitated out, and a considerable excess of thrombin formed.

Methods of Preventing Clotting.—In addition to the methods of making the blood incoagulable inside the body, *i. e.*, by stimulating

the out-pouring of heparin by injecting peptone (page 275), and by injecting hirudin (page 276), there are several ways of preventing shed blood from clotting. One is to draw the blood directly into a solution of a calcium precipitant (1 per cent sodium oxalate serves well[1]). Thrombin cannot form in the absence of calcium ions. Oxalated blood will clot if an excess of a soluble calcium salt is added to it. Hirudin added to shed blood prevents it from clotting provided enough is used to neutralize all the thrombin. Blood drawn into strong magnesium sulphate solution (1 part 27 per cent solution to 4 parts blood), will not clot, although a clot will form upon dilution with sufficient water. The strong salt solution appears to interfere with thrombin formation; at least "salted" blood can be made to clot by adding thrombin.

Blood drawn directly from the bloodvessels through a syringe needle coated on the inside with paraffin or oil, into a clean syringe similarly treated, will remain unclotted for an hour or so, a fact taken advantage of in blood transfusion (next page). The explanation appears to be that under this condition the platelets are preserved from rapid disintegration (page 263), and since contamination with the other source of cephalin, *i. e.*, the tissues, has been avoided the heparin will not be nullified, except slowly, and clotting will be much delayed. Snake venom injected into the blood stream interferes with clotting, presumably by destroying or neutralizing the cephalin, and so leaving the heparin unneutralized.

There is a somewhat uncommon disease known as *hemophilia*, in which the blood clots with such slowness that apparently insignificant hemorrhages are checked with great difficulty, or sometimes not at all, before a fatal loss of blood occurs. The only blood defect yet demonstrated is a marked increase in the resistance of the platelets to disintegration (Howell). A fact of great biological interest is that hemophilia is a sex-linked hereditary character. It is less common than another well-known sex-linked character, red-green color blindness (page 657), because of the high mortality associated with it.

Clotting in Vivo.—A fact of both theoretical interest and practical importance is that the equilibrium upset in blood when clotting begins is more stable when the blood is confined within the bloodvessels than when it is shed. This is apparently dependent on the higher total carbon-dioxide content of the blood in the vessels (page 274). A striking manifestation of the greater stability is seen in the fact that considerable quantities of pure thrombin or of defibrinated blood containing excess of thrombin can be injected directly into the vessels of animals with little danger of clotting,

[1] Sodium citrate has the same effect, although it does not precipitate the calcium. It acts by forming a double salt, sodium-calcium citrate, in which calcium ions are not present.

while adding either to blood outside the body hastens normal clotting decidedly. (To minimize danger of clotting when defibrinated blood is injected the fibrin mass should not have its fluid contents squeezed into the blood and the blood should stand on ice for twenty-four hours if possible.)

In contrast with the freedom from intravascular clotting on injection of thrombin is a considerable likelihood to it when cephalin is introduced. The reason for avoiding squeezing of the fibrin mass in preparing defibrinated blood (see above) is to lessen contamination with cephalin. Since the only known effect of cephalin is to facilitate formation of thrombin, this greater susceptibility is difficult to understand.

BLOOD TRANSFUSION.

In various diseases, and especially in severe hemorrhage, a highly desirable restorative treatment in theory is the introduction of an adequate quantity of normal blood into the patient's veins. This has been recognized for a long time, but attempts to realize the theory in practice have been successful only comparatively recently. One stumbling block to early efforts was the danger of thrombus formation. The early investigators knew no means of keeping the blood liquid except by defibrinating it, and, lacking detailed knowledge of the mechanism of clotting, failed to prevent contamination of the blood with cephalin. They were accordingly troubled with thrombi to a discouraging degree.

The introduction of blood transfusion as a practical procedure in human surgery dates from the development of a technique (Carrel) for temporarily anastomosing a vessel of a "donor" with a vessel of a "recipient" in such a manner that no surfaces except the tunica intima of the vessels come into contact with the blood as it flows from one set of vessels to the other. This procedure, while wholly successful surgically, is time-consuming, complicated and decidedly uncomfortable, both to donor and recipient. It has been generally superseded by a simpler method which consists of withdrawing the blood directly from the veins of the donor into an oiled or paraffined syringe (page 278), or into a syringe containing a small amount of sodium citrate, the quantity being just sufficient to combine with the calcium of the blood taken. This blood is then injected directly into the veins of the recipient.

On account of the frequent natural occurrence of various kinds of antibodies in blood (page 253), there is always the possibility that the blood of a potential donor may happen to contain agglutinins or even hemolysins for the blood of the recipient, or *vice versa*. This possibility is so apt to be realized when any other species than man is used as donor that blood transfusion is never now resorted

to in human surgery except from one human being to another. Even in the human species different blood strains exist in the sense that the blood of one strain may agglutinate the blood of another. It appears that there is little or no danger of *hemolysis* when normal human bloods are mixed, although if either donor or recipient is diseased hemolysins may be present. The chief danger in practice is that the serum of the recipient may agglutinate the corpuscles of the donated blood. The resulting corpuscle clumps may block small vessels precisely as thrombi are apt to do. This danger is avoided by testing the blood of recipient and prospective donor beforehand to make sure that no so-called *iso-agglutinins* are present. It has been found that human beings fall into four main groups in respect to the agglutinative tendency of their blood. Transfusion from one individual to another within a given group is perfectly safe so far as danger of agglutination is concerned.

Summary.

The quantity of blood in the body can be estimated by the direct (Welcker) method, which consists essentially of bleeding, followed by washing out of the vessels, and correcting for the amount of liquid used in washing; or by an indirect method, which consists of introducing into a vein a known quantity of an easily detectable substance, allowing time for thorough mixing, and then determining the amount of the substance per unit quantity of blood. Estimates of the amount of blood in the human body by the direct method (2 determinations) place it at 7.7 per cent of the body weight; by the indirect method (vital red or carbon monoxide) 5 per cent.

The relative constancy of blood volume depends mainly on the maintenance of an equality between the intake and outgo of water. Osmotic pressure and filtration pressure are forces that may cause water to leave the circulation. The effectiveness of filtration pressure varies directly with the filtration permeability of the capillary walls and inversely with the viscosity of the blood. The entry of water into the circulation appears to depend mainly on osmotic pressure; the osmotic pressure of the blood colloids is looked upon as particularly significant. The mechanism by which blood volume is restored after hemorrhage is not understood.

A rough estimate of the distribution of blood in the body places about 40 per cent in regions from which diversion into other regions does not occur; these regions are the heart, lungs and large blood-vessels and the vessels of the central nervous system. The remaining 60 per cent of the blood is estimated to be mainly in the skin, the skeletal muscles and the splanchnic area, regions in which a certain amount of diversion of blood from one to another occurs in satisfying the varying metabolic needs of different parts of the body.

Clotting of blood consists essentially of the precipitation of plasma fibrinogen in the form of a meshwork of minute *fibrin* needles. The conditions governing clotting are such as to bring on the process automatically whenever there is rupture of a bloodvessel, and to prevent it from happening (*thrombus* formation) so long as the circulation is intact. Clotting time is a function of total CO_2 content of blood, being at the minimum at about 30 per cent, and becoming progressively longer as the CO_2 percentage is increased.

In ordinary hemorrhage the blood flows over tissues extraneous to it. The normal clotting time, under this condition, is three to ten minutes in man and most mammals. When all contact with tissues is carefully avoided the clotting time is one-half hour or more.

The clotting is due to a reaction between plasma fibrinogen and *thrombin* to form fibrin. Thrombin is not present as such in the circulating blood, but is represented by a precursor, *prothrombin* (proserozyme). Two main theories of thrombin formation are indicated diagrammatically on page 277.

Evidence indicates the presence in blood of small amounts of two anticoagulants. The first, *heparin*, prevents the reaction between prothrombin and calcium by which thrombin is formed; the second, *antithrombin*, prevents the interaction between plasma fibrinogen and thrombin by which fibrin is formed. The action of heparin is neutralized by cephalin; that of antithrombin by thrombin (formation of *metathrombin*).

Blood in the body may be made non-coagulable by injecting a peptone solution, which stimulates out-pouring of heparin by the liver; also by injecting snake venom, which is thought to destroy the cephalin and so leave the heparin normally present unneutralized.

Shed blood can be prevented from clotting by drawing it directly into a solution of a calcium precipitant, or into a strong solution of magnesium sulphate, or for a time by drawing it without contact with tissues and under conditions favorable to the preservation of the platelets (diminished influence of cephalin). Antithrombin (*hirudin*) in quantity prevents clotting both within the vessels and in shed blood.

In the disease *hemophilia* blood clots with extreme slowness, due, apparently, to a marked increase in the resistance of the platelets to disintegration.

Successful blood transfusion depends: (1) On the prevention of clotting, a matter of minimizing cephalin liberation, or of precipitating out the calcium from the donated blood; (2) on avoiding an admixture of bloods that might hemolyze or, more probably, agglutinate one another. Human beings fall into four main strains in respect to the agglutinative tendency of their blood. Transfusion within a strain is free from danger of agglutination.

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CHAPTER XVIII.

CIRCULATION: VOLUME, CIRCULATORY APPARATUS, HEART.

UNIT CIRCULATION.

In Chapter XV is a general statement of the function of the circulation. The conditions to be realized, either completely or approximately, are shown to be: (1) Blood flow through the capillaries of the tissues, adequate in volume for meeting the metabolic requirements of the latter, moment by moment, and hence susceptible of adjustment from moment to moment as these requirements change; (2) blood flows through the different maintenance systems, respiratory, digestive, hormone-contributing, excretory and temperature-regulating, adequate, in turn, for the renewal of the blood at even pace with the demands upon it.

Obviously the most significant data of the circulation are those on the quantity of blood delivered per unit of time, either to the body as a whole or to individual capillary areas. The minute is the convenient time unit, hence the figures commonly used are those of *circulation volume per minute*, or briefly, *unit circulation*. In the body, as a whole, the unit circulation for any period is the product of the average number of heart beats per minute for that period by the average amount of blood discharged from the left ventricle of the heart at each beat (this latter is designated *stroke volume*). For each individual capillary area the unit circulation is that proportion of the total circulation which flows through it in a minute.

Determinations of Unit Circulation.—The principle on which all practicable methods of obtaining total circulation volume in man are based was enunciated by Fick. It can be illustrated as mediated by oxygen, as follows: If from the amount of oxygen in each milliliter of blood passing through the left heart (cardiac arterial blood) be subtracted the amount in each milliliter of blood passing through the right heart (cardiac venous blood) the difference gives the amount taken up per milliliter by the blood in its passage through the lungs. This quantity divided into the total uptake of oxygen from the lungs during any given time gives the volume of blood passing through the lungs during that same time. This is, of course, equivalent to the volume moving through the general circulation in the same period. Instead of oxygen carbon dioxide may be used

as the test substance. In this case the quantity per milliliter cardiac arterial blood is subtracted from the quantity per milliliter cardiac venous blood to obtain the divisor, and the dividend is the *output* of CO_2 per unit of time. Any respirable gas that is taken up by the blood is theoretically usable for making determinations, the data being handled precisely as in the case of oxygen.

This principle, simplicity itself in theory, is translated into practice only with great difficulty and considerable uncertainty. Of the three factors involved, only one, the uptake or output of the test gas per unit of time is readily determinable. It is possible to determine the gas content of cardiac arterial blood by analyzing any arterial blood sample, since no significant change occurs during the passage of the blood from the heart to any peripheral artery. But it is obviously not often practicable to take human arterial blood samples for analysis. Cardiac venous blood cannot be obtained from human beings. Only cutaneous veins are accessible for blood withdrawal, and their gas content is not, except by accident, similar to that of the mixed venous blood entering the heart from all parts of the body. It follows that in practice the Fick method requires the gas contents of arterial and venous blood to be computed from data obtained by other means than taking blood samples.

The method of Bock uses respiratory CO_2 as the test gas. The CO_2 content of arterial blood is found by analyzing a sample of the air in the alveoli of the lungs (page 369). This air has been shown to be in gaseous equilibrium with the arterial blood whenever the subject is at rest and breathing normally. Consequently the CO_2 *pressure* in the alveolar air equals the CO_2 *tension* in the arterial blood (page 214). To find the CO_2 content of cardiac venous blood the following procedure is resorted to: The subject breathes deeply into and from a reservoir of 4 to 5 liters' capacity filled with oxygen to which has been added 5 or 6 per cent of CO_2, thus bringing it into approximate equality with the CO_2 content of the venous blood. After the subject has breathed into the reservoir four or five times the CO_2 pressure in his alveolar air comes into equilibrium with the pressure of the same gas in the bag, which pressure then equals the CO_2 *tension of the venous blood* because the presence of CO_2 in the air breathed prevents the CO_2 from escaping from the blood into the alveoli as it normally would (page 364). The air in the reservoir is then analyzed for its CO_2 pressure. The conversion factor for rendering the difference in CO_2 tensions between venous and arterial blood into the difference in actual CO_2 content is 3.3. The tension difference multiplied by this figures gives, therefore, the figure which is divided into the total CO_2 output per unit of time (separately determined) to find the circulation volume.

Another application of the Fick principle has been devised by

Y. Henderson and Haggard, and is perhaps the most convenient yet proposed. It consists of breathing an atmosphere containing a small proportion of ethyl iodide vapor and determining the amount taken up by the blood per minute. If the solubility of ethyl iodide in blood is known a simple computation then gives the amount of blood that must have passed through the lungs in a minute, in other words, the unit circulation. In practice the data to be obtained are: (1) The number of liters of air inspired per minute; (2) the concentration of ethyl iodide in this air; (3) the concentration of the same substance in the expired air; (4) the concentration of the iodide vapor in alveolar air. From the first three figures the *total uptake* of ethyl iodide by the blood can be computed. The fourth gives a means of determining the amount of iodide taken up *per unit volume of blood*, the iodide tending to distribute itself volumetrically between blood and alveolar air in the ratio 2 to 1. The peculiar advantage of ethyl iodide for the determination is that accurate estimations of the relatively minute amounts in the various air samples are readily made. A second advantage claimed by Henderson and Haggard, but questioned by some other investigators, is that all the iodide entering the arterial blood is presumed to be promptly taken up by the tissues and decomposed, so that none returns to the lungs in the venous blood to complicate the measurements. In a series of determinations on normal adult males at rest Henderson and Haggard found the unit circulation to average about 100 ml. per kilo body weight; the extremes were 91 and 126 ml. This corresponds to a total average unit circulation in a 70-kg. man, of about 7000 ml., with a range of between 6400 and 8800 ml.

The only direct determinations of unit circulation through individual capillary areas that have been made in man depend on one of two methods, either that of Stewart, in which the heat given off to a calorimeter per unit of time is used as a basis for calculating the blood flow, or that of Brodie, *etal.*, in which the increase in volume of a part, immediately following the sudden closure of its venous outlet, is used for calculating the flow. These methods are applicable only to the extremities, since the part to be investigated must be capable of being placed in a calorimeter in the first of them and in an apparatus for registering volume changes (plethysmograph) in the second.

In experimental animals various methods have long been available for determining the unit circulation through the arteries supplying individual organs or regions. The simplest, in theory, is one in which the artery is cut open and some sort of meter introduced. Various ingenious meters have been devised. The essential features of those that are successful are: (1) That they measure accurately the flow of blood through them; (2) that they do not

interfere with the normal flow, so that what is registered is a true and not a distorted value. The first instrument for this purpose was designed by Ludwig and called by him a *stromuhr*. The same name is commonly applied to other instruments devised since to the same end. Some data obtained by stromuhr readings are used in the table on page 348.

Capillary Pressure.—Of less importance than circulation volume, but still of much significance, is the small, but definite, hydrostatic pressure obtaining in the various capillaries. This is important in that the filtration of the liquid part of the blood out into the tissue spaces (page 357), the action of the kidney glomeruli (page 144) and probably that of gland cells in general (page 136) depends in part on the hydrostatic pressure of the blood in the appropriate capillaries. It has recently been shown (Landis) that the rate of escape of fluid through the capillary walls varies directly with the capillary pressure. (For data on capillary pressure, see page 342.)

SUBDIVISIONS OF THE CIRCULATORY APPARATUS.

Heart and Arteries.—In order to develop a clear picture of the way in which the circulation operates to maintain adequate circulation volume and sufficient capillary pressure in all parts of the body, it is desirable to outline the successive structural regions into which the system as a whole is subdivided. We note first the presence of a reciprocating pump, the *heart*, alternately being filled from the veins and discharging by its own muscular contractions into the *arteries*. These latter consist, essentially, of a system of highly elastic, strong-walled tubes ramifying to all parts of the body and subdividing repeatedly in tree-like fasion. Wherever an artery branches the cross-section of the branch plus the main artery is always greater than the artery before branching. The effect of this is that as the arterial bed subdivides it widens, the total cross-section becoming progressively greater as the peripheral vessels are approached. Branching is much more frequent in and near the peripheral tissues than elsewhere. It follows that the major part of the widening occurs near the periphery. Hand in hand with the progressive widening of the arterial bed as a whole goes a progressive narrowing of the individual vessels. The nearer one approaches the periphery the smaller are the arteries.

In nearly all parts of the body the smaller arteries anastomose abundantly. The arterial path, so far as most individual organs are concerned, consists, not of a set of independent channels, but of a series of meshworks of intercommunicating vessels. The arteries that feed an organ open into a primary meshwork, in which the arrangement of vessels is often strikingly regular. From the primary meshwork a secondary meshwork of finer arteries usually

branches off. From the secondary meshwork the arterioles may spring directly, or a third meshwork may intervene. In the heart, brain and kidneys the arteries do not anastomose but each carries the entire blood supply to a particular region. The effect of occlusion of one of these "terminal" arteries, as by a thrombus, is obviously much more serious than of occlusion of an anastomosing artery.

Arterioles.—As the arteries become so small that they begin to be difficult to make out with the naked eye the structure of their walls is found to differ from that of the larger arteries in that instead of elastic tissue being predominant and smooth muscle incidental, smooth muscle becomes predominant and elastic tissue relatively incidental. The effect is that while the caliber of the larger vessels can only be altered by changing the hydrostatic pressure within them, the caliber of the small arteries is determined mainly by muscular action under the control of autonomic nerves (page 128). In the finest arteries, designated as *arterioles*, it is probable that neuromuscular control of caliber is complete, elastic tissue being virtually wanting. On account of their minute size the arterioles offer marked frictional resistance to the flow of blood through them. There is, of course, a certain amount of frictional resistance to the movement of the viscous blood all along its path, but the resistance offered by the microscopic vessels is so much greater than that offered by the larger vessels that relatively little account need be taken of the latter. The inside diameter of the arterioles probably ranges from about 10 μ up to 40 or 50 μ.

Capillaries.—Every arteriole terminates in several capillaries. The average number of capillaries to an arteriole is not known. It probably differs in different tissues. The fundamental distinction between arterioles and capillaries is that the capillary walls permit of interchanges of material by osmosis, dialysis and filtration, while the arteriole walls do not, there being sufficient muscular tissue present to prevent interchanges from taking place. In the capillaries muscular tissue is reduced to occasional cells, known as *Rouget* cells, scattered along the capillary wall proper, which is simply the endothelial lining of the vascular system extending into these finest subdivisions. It is known that individual capillaries may be closed entirely or opened to their full extent (Fig. 28). There is evidence also that closing and opening are subject both to nervous regulation and to chemical influences brought to the capillaries by the blood (page 341). Whether the changes in capillary diameter are due to the action of the Rouget cells or to contractions and relaxations of the endothelial cells is not yet certainly known.

The capillaries are as small as, or smaller than, the smallest arterioles; their average inside diameter is given as about that of a red corpuscle, *i. e.*, about 8 μ (page 261). On account of their small caliber they share with the arterioles in interposing great

frictional resistance to the flow of blood through them. The total number of capillaries in the body is so enormous that figures have

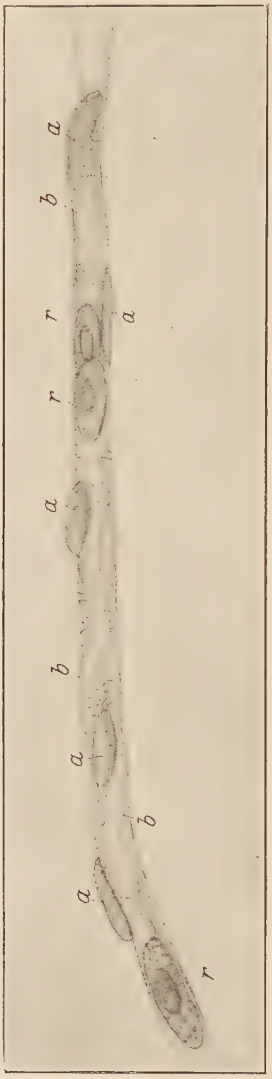


Fig. 28.—Capillary from nictitating membrane of frog (after Vimtrup). *a*, Rouget cells; *b*, nuclei of endothelial cells; *r*, red corpuscles. (Krogh; Anatomy and Physiology of Capillaries, Yale University Press.)

little meaning. Krogh has compiled data for several tissues, including skeletal muscle. The number per square millimeter of muscle cross-section varies in mammals, in general, inversely with

the size of the mammal. Counts around 1350 are reported for the horse and 2630 for the dog, indicating for man a figure around 2000 per square millimeter. The average length of capillaries does not exceed 0.5 mm. (Krogh). It follows that each cubic millimeter of skeletal muscle contains on the average something like 4000 capillaries. Assuming the total musculature to be 40 to 45 per cent of the body weight (Vierordt) a 70-kg. man has about 30 kg. muscular tissue, hence he has in his muscles alone 4000 × 30,000,000, or 1.2×10^{11} capillaries. Easier to grasp, and of equal practical significance, is the fact that there are probably more than three times as many capillaries as muscle fibers in any given cross-section of skeletal muscle.

From the average capillary diameter and length, and total capillary number, as given above, the approximate capacity of the muscle capillaries can be calculated. It works out at about 1500 ml. The muscles make up not more than two-thirds of the vascular tissues, hence an estimate of 2000 ml. for the capillary capacity of the whole body is undoubtedly conservative. It should be noted, however, that even this conservative estimate assigns to the capillaries alone a sufficient capacity to contain more than one-half of all the blood in the body (page 270). A crucial fact about the capillaries, which must be thoroughly appreciated if the circulation is to be understood, is that in the skeletal muscles and some other tissues, including the walls of the stomach and intestines and the kidneys, fewer than 1 in 10 of the capillaries are open simultaneously when the tissues are inactive, and many that are open are contracted below the average diameter stated above (Krogh). It follows that in these tissues during periods of quiet only a small fraction of the potential capillary capacity is actually occupied with blood. The *functioning* capillary capacity of the resting body is thus very much less than the potential capacity. Only very rough guesses can be made as to the actual value of this functional capacity. A guess that attempts to be an underestimate rather than the reverse assigns 200 to 250 ml. as the possible range. The only justification for any sort of guess is that capillary capacity is the determining factor in velocity of capillary blood flow (page 322), and this latter is an important factor in the efficiency of the gaseous interchange (page 218).

During activity of the surrounding tissues and in traumatic shock many or all of the capillaries open out widely, increasing materially the functional capacity of the capillary bed as a whole. The consequences to the circulation and to tissue nutrition are discussed elsewhere (pages 341 and 350).

Venules.—The capillaries merge into *venules*. These are microscopic tubes differing from the capillaries with which they are continuous in having a layer of connective tissue outside the endo-

thelium. This additional layer is thought to make the venules impermeable, thus definitely restricting to the capillaries interchanges of material (Krogh questions this restriction in at least one tissue, the skin). The venules share with arterioles and capillaries the property of contracting and relaxing.

There is no smooth muscle coat such as the arterioles have. The contractions and relaxations are essentially similar to those of capillaries, both in nature and control, the latter being exercised in part by nerves and in part by chemical substances brought to the venules in the blood. The venules in most parts of the body anastomose freely, thus enabling the blood as it flows from the capillaries to follow any one of various paths on its way to the large veins.

Veins.—The blood returns from the venules to the heart in the *veins*. The venous system, as a whole, shows an arrangement similar to that of the arterial tree, but since the direction of movement of the blood in the veins is toward the heart, the system is thought of as *converging* into a narrower and narrower bed, precisely opposite to the constant widening out of the arterial channel. It is true, probably without exception, that the veins at any given distance from the heart have larger caliber than the corresponding arteries. The total cross-section of the venous channel is thus greater, level by level, than of the arterial channel. Of great significance to the flow of blood through the veins is the presence of valves at frequent intervals along all except the large veins of the trunk. These valves open always toward the heart, and so prevent any backward flow of blood. The veins are readily distensible, adapting their caliber to the quantity of blood to be accommodated without offering much elastic resistance. The veins have a certain amount of smooth muscle tissue in their walls. This tissue is undoubtedly important in the small veins (page 343), probably in the larger as well.

THE HEART.

The first structure of the circulatory system to come up for consideration is the heart. Structurally this is a double pump, each unit consisting of two chambers, the *atrium* (auricle) and the *ventricle*. The relations of the chambers to each other and to the other parts of the circulation are indicated diagrammatically in Fig. 29.

The heart is composed primarily of cardiac muscle tissue (page 94). The arrangement of the muscular elements is such that when the heart is beating normally both atria contract together and both ventricles together. Any account of the action of one side is therefore applicable in general to the other. One must bear constantly in mind, however, that the inflow into the right heart

is from the systemic veins (venæ cavæ) and the outflow into the pulmonary artery while the inflow into the left heart is from the pulmonary vein and the outflow into the great systemic artery (aorta). It must also be remembered that the left ventricle sus-

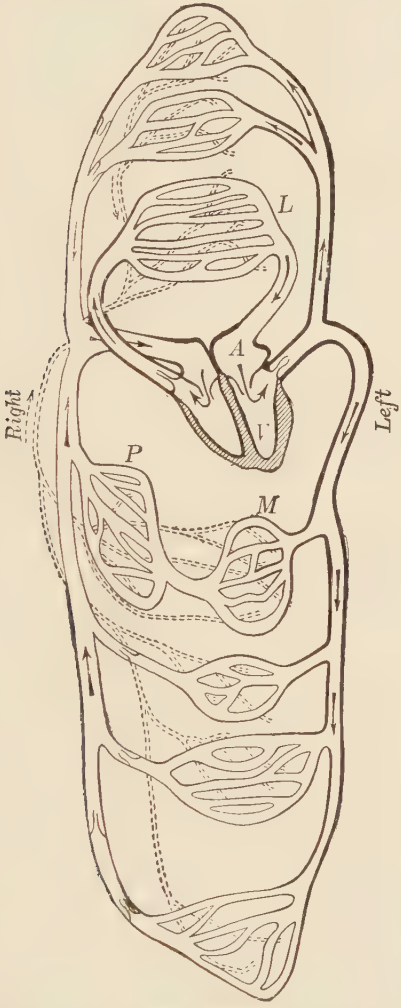


FIG. 29.—Diagram of the circulation, illustrating the course of the blood through the heart. *A*, left atrium; *V*, left ventricle; *L*, lung; *M*, upper part of gastro-intestinal tract; *P*, liver. Dotted lines represent lymphatic vessels. (Martin's Human Body, Henry Holt & Co., Publishers.)

tains the general (systemic) circulation, while the right ventricle has only the task of forcing blood around the pulmonary circuit. Corresponding with this difference in task is a marked difference

in thickness of muscular wall, and so in force of beat. The *volume of blood* ejected per beat is the same in each side of the heart, as must be to prevent blood from piling up either in the systemic or the pulmonary circuit.

The Pacemakers.—Sino-atrial and Atrio-ventricular Nodes.—All portions of the mammalian heart possess the property of *automatic rhythmicity*. As already pointed out, however (page 95), there is an inverse relation in different parts between the display of rhythmicity and the power of contracting forcibly. The two regions that

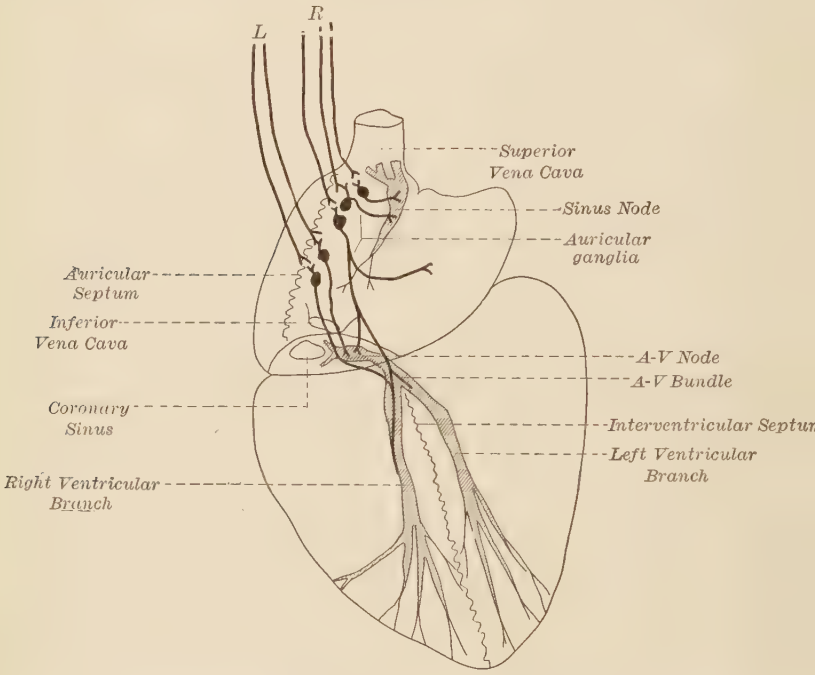


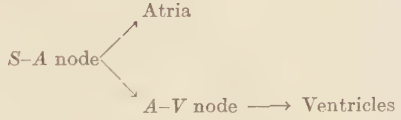
FIG. 30.—Diagram showing pacemakers and conducting system of the heart (Wiggers). *R* and *L* represent cardiac nerve fibers in right and left vagus respectively (Wiggers' Circulation in Health and Disease.)

are most rhythmic, and so act as pacemakers for the whole heart, are virtually non-contractile. One such region is located in the musculature of the posterior part of the atrium between the openings of the superior vena cava above and the coronary sinus below. This is a club-shaped mass of cells, readily distinguishable histologically from the surrounding atrial musculature. It is known as the *sino-atrial (S–A) node*, also as the node of Keith and Flack. It is a vestige of the *sinus venosus*, which in lower vertebrates is the first in sequence of the contractile chambers of the heart. The

second pacemaker is the *atrio-ventricular* (*A–V*) node, lying at the posterior and right border of the interatrial septum. This cell mass, also readily distinguishable histologically, is in part a sinus vestige, like the *S–A* node, and in part derived from tissue of the *auricular canal.*

The His-Tawara Conducting System.—The *A–V* node merges into a strand of specialized tissue, composed largely of so-called *Purkinje cells,* which strand passes across the atrio-ventricular septum as the *atrio-ventricular bundle,* or "His-Tawara bundle." This bundle is the sole conducting path across the atrio-ventricular septum, at least in man. Upon its integrity hinges the coördinated beating of the heart. The atrio-ventricular bundle divides into two main strands, one to the musculature of each ventricle. These main strands subdivide into numerous arborizations which terminate in relation with contractile cells of the ventricle on its inner aspect. The whole makes up the His-Tawara conducting system of the heart (Fig. 30).

Initiation of the Beat.—In the normal heart the initiation of each beat is due to an automatic disturbance of equilibrium in the *S–A* node. This disturbance spreads with great rapidity throughout both atria, involving all the contractile fibers of both in less than 0.05 second. In the course of its spread the disturbance also involves the *A–V* node, upsetting the equilibrium in it, although there is a delay of about 0.05 second before this *A–V* node disturbance gets under way. From the *A–V* node the disturbance spreads over the His-Tawara bundle to the inner surfaces of both ventricles, and thence from one ventricle muscle fiber to another until all are excited to contraction. The arborizations of the conducting system are so distributed that all parts of both ventricles come into action within a few thousandths of a second of one another (so far as the action of the heart is concerned, practically simultaneously), and about 0.11 second after the initial discharge of the *S–A* node. Both the atria and the ventricles are dependent on the *S–A* node for their normal excitation, but the latter receive it indirectly by way of the *A–V* node. The arrangement may be indicated as follows:



The Refractory Period.—The fact that cardiac muscle has a well-marked *refractory period* is stated and discussed on page 95. The significance of this in connection with the action of the pacemakers is that following the upset of equilibrium in any cardiac tissue there

is always a delay before another upset can occur. That tissue which has the shortest refractory phase is the first one to recover to the discharge point and so automatically becomes the pacemaker. The tissues slower to recover will always be excited from the pacemaker before their own rhythmicity develops, and so will always be in a refractory condition at the time they would have gone into action spontaneously. The recovery of the *S–A* node is slightly quicker than of the *A–V* node. This makes the former the normal pacemaker. Not much depression of the one or whipping up of the other is needed, however, to reverse the order of recovery and so make the *A–V* node pacemaker. This reversal has frequently been demonstrated experimentally. It probably occurs clinically in some instances.

Premature Contraction and Compensatory Pause.—Cardiac tissue is like nervous tissue in that the refractory period as a whole includes both an absolute and a relative phase (page 106). During the relative phase recovery is going on; in other words, the former equilibrium is being restored. In heart tissue, as in nerve tissue, sufficiently strong stimulation will cause a response during the relative refractory phase, and such a stimulation and response will leave the usual refractory period in their train. It may easily happen that the ventricles, which are beating regularly in response to excitations from the nodal tissue, receive from some other source a stimulus so timed as to fall in a relative refractory phase, and strong enough to cause response. The contraction thus produced is ahead of the regular order, and so is a "*premature contraction*" (extrasystole; page 312). The refractory phase following a premature contraction usually lasts long enough so that the ventricles cannot respond to the next regular excitation from the *S–A* node. There is thus a pause until the next succeeding discharge of the node, when the ventricles resume their normal rhythm. This pause is known as the *compensatory pause*. The expression is a misnomer so far as any particular compensation for extra activity is implied; the pause is merely the wait for a stimulus to arrive after the ventricle has recovered sufficiently to become responsive. The first contraction after such a pause is usually more vigorous than the regular beats at the time. The explanation appears to be that in the normal sequence the interval between nodal discharges is too brief for the ventricular tissue to recover to its maximal extent, and so it beats regularly at less than its potential force.

Flutter and Fibrillation. As already pointed out (page 96) there is free conductivity of excitation from fiber to fiber in cardiac tissue. Since the two atria on the one hand, and the two ventricles on the other, are hollow structures with continuous walls, it would seem possible for an excitation wave once established in either the atria of the ventricles to travel round and round, exciting successive

ranks of fibers indefinitely. The reason this does not happen in the normal heart is that the speed of conduction is high enough and the refractory phase long enough so that when any excitation wave that may pass around either pair of chambers reaches its starting point the fibers there have not yet recovered, and so the wave is extinguished. Abnormal conditions may so shorten the refractory phase in a particular ring of tissue that an excitation wave will actually travel round and round indefinitely. This is seen clinically, particularly in the atria. The closed path through which the excitation travels is referred to as a "circus ring." From this ring excitation is conducted to the other fibers of the atria. In the condition known as "flutter" the excitations from the ring are so spaced that the entire atria contract in coördinated fashion, but very much more frequently than in normal beating. In "fibrillation" the different parts of the ring discharge in an irregular sequence and the resulting contractions of the atrial fibers are incoördinated. Phenomena corresponding to the above are theoretically possible in the ventricles, and may be observed under experimental conditions. They are rarely seen clinically because coördinated and reasonably slow contractions of the ventricles are essential to life. Patients developing either flutter or fibrillation of the ventricles seldom live long enough for the condition to be observed, except hurriedly and incidentally.

Heart-block.—The coördinated beat of the atria and ventricles in regular sequence depends on the integrity of the conducting paths of the heart. If these paths are interrupted, as they may be by disease, by functional impairment, as in anoxemia, by certain drugs, as digitalis and epinephrine, and in experimental animals by local application of cold, by cutting, or by mechanical compression, there is an interference with coördinated beating. The condition is known as *heart-block*. Since the conducting path may be interrupted at various places, and the block may be either partial or complete, various types are possible.

In partial block some of the excitation waves pass the block, others fail to pass. There is usually a regular rhythm, some definite ratio obtaining between the waves that pass and those that drop out. If the partial block is between the *S A* node and the atrial tissue (*sino-atrial block*) the condition is evidenced by the fact that the heart in an otherwise normal rhythm misses one or more complete beats at regular intervals. In partial block between the *A V* node and the ventricle (*atrio-ventricular block*) the atria beat normally; the ventricles do the same, except that at regular intervals ventricular beats fail to develop as they should. Sometimes every eighth or every fourth or every second excitation wave fails to pass the block, while all the others do so. In other cases only one in three or one in four passes. The salient feature of partial block is

that all such beats as do occur fall into their proper sequence (except that following a missed beat conduction over the His-Tawara bundle is usually slightly quickened, causing the next contraction to occur a small fraction of a second early).

In complete block the regions cut off from the influence of the *S–A* node beat in accordance with the inherent rhythmicity of their most rhythmic part, contracting and relaxing in a rhythm that has no relation to that shown by regions still under *S–A* node influence. This independent rhythm is slower, often much slower, than that of the normal heart, as is to be expected from what has already been said of the relative rhythmic properties of the nodal and the highly contractile tissues (page 292). Complete *sino-atrial block* in man is difficult to distinguish from a normally slow heart, since evidence that the *S–A* node is discharging normally, but failing to have the excitation waves it sets up reach the atria and the *A–V* node, is not easy to obtain. In complete *atrio-ventricular block* diagnosis is usually easy, because the atria continue to beat at the usual rhythm while the ventricles show a slow rhythm not related in sequence to the rhythm of the atria.

In the milder degrees of heart-block there is no demonstrable impairment of the circulation. In severer degrees impairment is demonstrable, but even in complete atrio-ventricular block, is ordinarily not enough to interfere with the delivery of the quantities of blood necessary for the normal metabolism of the inactive body. The situation becomes quite different, however, when vigorous exercise is undertaken, for an increase in heart-beat is an important factor in maintaining augmented metabolism (pages 305 and 349), and the primary mechanism for increasing the heart-beat operates through the sino-atrial and atrio-ventricular nodes (page 301). When the mechanism for increasing the heart-beat is set in play the pacemakers discharge more frequently, and usually more vigorously, than before. The atria and ventricles follow this increased discharge, or fail to follow it, according to the position and completeness of the block. If the atria follow and the ventricles do not, as happens in complete *A–V* block, the incoördination already present is obviously exaggerated, so that instead of an improvement in circulation to meet the increased metabolic needs of the body there may actually be a further impairment. A block that is only partial at the cardiac rhythms of the inactive body may become complete at the faster rhythms set up in the nodes in bodily exercise. Thus a fairly coördinated beat may be converted into one that is incoördinated. Any degree of block severe enough to permit either of these things to happen obviously limits decisively the ability of the circulation to meet augmented metabolic requirements.

Electrocardiograms.—In Chapter V, page 71 the fact is stated

that the excitation process in tissues is accompanied by a lowering of electrical potential, so that if an excited region is connected electrically with an unexcited one an "action current" will flow from the latter to the former. Excitation in the heart spreads from the *S–A* node in the manner described above (page 292), successive areas taking on a lowered potential as the wave advances, and returning to their former potential as it passes beyond them. If one leading-off electrode is placed on or near the *S–A* node of a beating heart and another on the ventricle, the two being in circuit with a sensitive electrometer (the string galvanometer as adapted for the purpose by Einthoven by preference), these potential changes can easily be demonstrated. In mammals they are of sufficient magnitude to affect the potential of the whole body. This fact is taken advantage of for obtaining records of the potential variations of the human heart, beat by beat; such records are known as *electrocardiograms*. To obtain them to advantage the two leading-off electrodes should be applied to the body in such positions that one is related to the base of the heart, the other to its apex. In practice three electrode arrangements are used, as follows:

Lead I—right arm, left arm.
Lead II—right arm, left leg.
Lead III—left arm, left leg.

As one would anticipate from the position of the heart in the body Lead II gives maximal potential differences.

Electrocardiograms are made by photographing the movements of the galvanometer string on a film moving at known speed. The galvanometer is so connected that a rise in the curve indicates that the lead on the basal side of the heart has a lower potential than the one on the apical side. Illustrations, showing the curves obtained by the use of the different leads are given in Fig. 31. The potential differences registered are those of the entire body, as set up by the sweep of the excitation wave over the heart, and are accordingly not simple. In fact the interpretation of the various waves, and especially the determination of their relationship to the contractions of the atria and ventricles present great difficulty. In general, one may say that the atria begin to contract near the middle of the *P*-wave and finish contracting at or very near the beginning of the *R S*-wave. The *R-S*-wave is attributed to the sweep of excitation over the ventricles. It accordingly comes an instant before the mechanical act of ventricular contraction gets under way. The *T*-wave comes during the latter part of ventricular contraction, while blood is being expelled from the ventricles into the large arteries. Characteristic electrocardiograms from cases of sino-atrial and atrio-ventricular block are reproduced in Fig. 32.

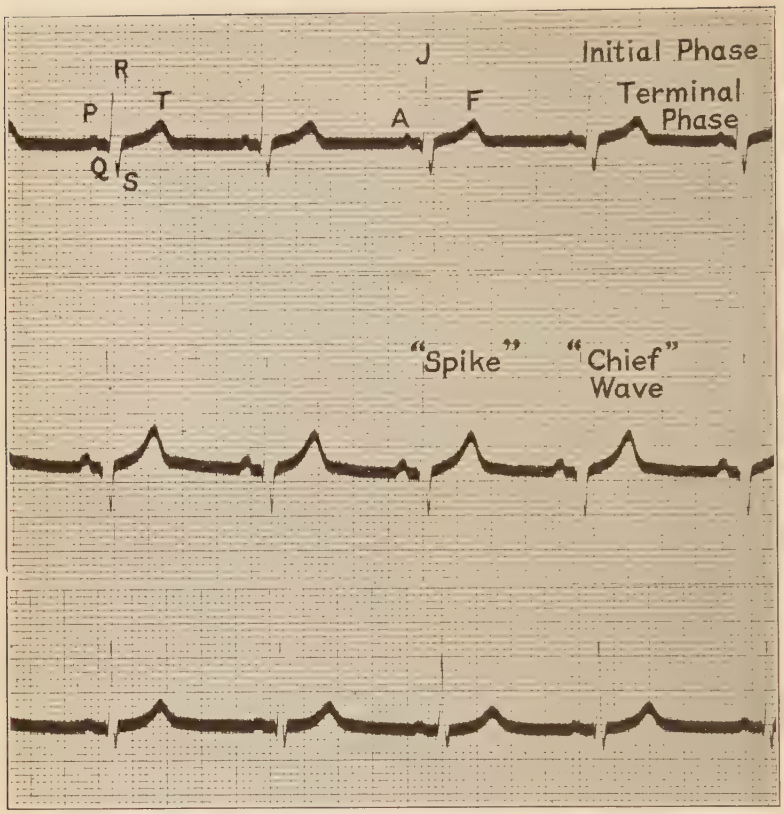


FIG. 31.—Normal electrocardiograms from the same individual, using Leads I, II and III. Each horizontal space = 0.04 second; each vertical space = 10^{-4} volt (H. B. Williams). (Wiggers' Circulation in Health and Disease.)

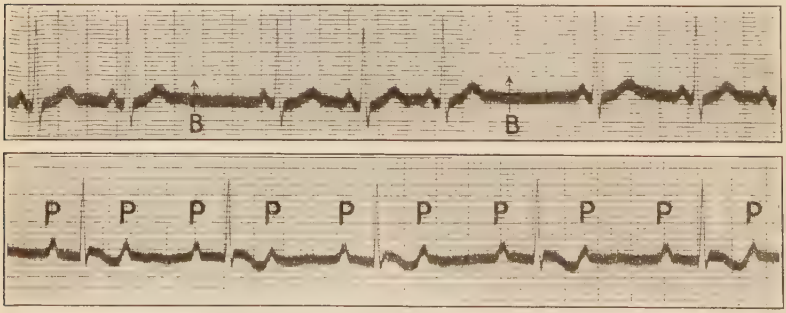


FIG. 32.—*A*, electrocardiogram from a case of sino-atrial heart-block (H. Feil); at B a complete complex drops out; *B*, a case of 2 to 1 atrio-ventricular block (R. Scott); every other *R–S* wave is missing. (Wiggers' Circulation in Health and Disease.)

NERVOUS REGULATION OF CARDIAC ACTIVITY.

The heart has double autonomic innervation. The general plan of organization of the autonomic system has already been described (page 128). That part of it which has to do directly with the heart consists of two "centers" within the central nervous system, and two autonomic nerve paths, one from each center, over which nervous impulses pass to the heart. The *cardio-inhibitory* center is located in the nuclei of origin of the vagus nerves. It appears to be a bilateral center, lying partly in the nucleus of the right, and partly in the nucleus of the left vagus. The path of conduction from it to the heart belongs to the bulbar outflow of the parasympathetic system (page 130), extending from the medulla to the heart by way of the *vagus* nerves.

The *cardio-augmentor* center cannot be located anatomically. It is thought to be a diffuse center, *i. e.*, to consist of scattered cells. Indirect evidence indicates that it is somewhere in the medulla. Its paths of conduction to the heart are over the sympathetic (thoracico-lumbar) system. They pass by way of white rami from the thoracic portion of the spinal cord to the stellate ganglia, thence to the inferior cervical ganglion of each side by way of the corresponding annulus of Vieussens. From each inferior cervical ganglion filaments composing the "cardiac plexus" pass to the atrial portion of the heart. The arrangement in the dog is shown in Fig. 33. That of man is said to be similar (Dogiel). Cannon and associates have shown that in the cat additional augmentor fibers pass from thoracic sympathetic ganglia as far back as the ninth in some animals. The vagus axons terminate in synaptic connection with ganglion cells imbedded within the heart substance. They are, therefore, "preganglionic" (page 129). The "postganglionic" fibers appear to be distributed chiefly to the *S–A* and *A–V* nodes, to the His-Tawara conducting system and to the fibers of the atria. The sympathetic axons that reach the heart are "postganglionic," arising from ganglion cells, either in the inferior cervical or the stellate ganglia. They are distributed in part to the nodes and in part, apparently, to the musculature of the heart itself, both atrial and ventricular. Since nicotine has the property of abolishing conductivity between preganglionic and postganglionic neurons, the action of the vagi can be ruled out by applying nicotine directly to the heart. A similar action on the sympathetic innervation can be obtained only if the nicotine is applied to the inferior cervical and stellate ganglia.

Inhibition and Augmentation.—The action of the parasympathetic (vagus) innervation on the heart is *inhibitory*, *i. e.*, tending toward decrease or abolition of activity. That of the sympathetic innervation is *augmentor*, *i. e.*, tending toward heightening of activity.

There are at least five factors in the complex functioning of the heart on which inhibition and augmentation can exert influence.

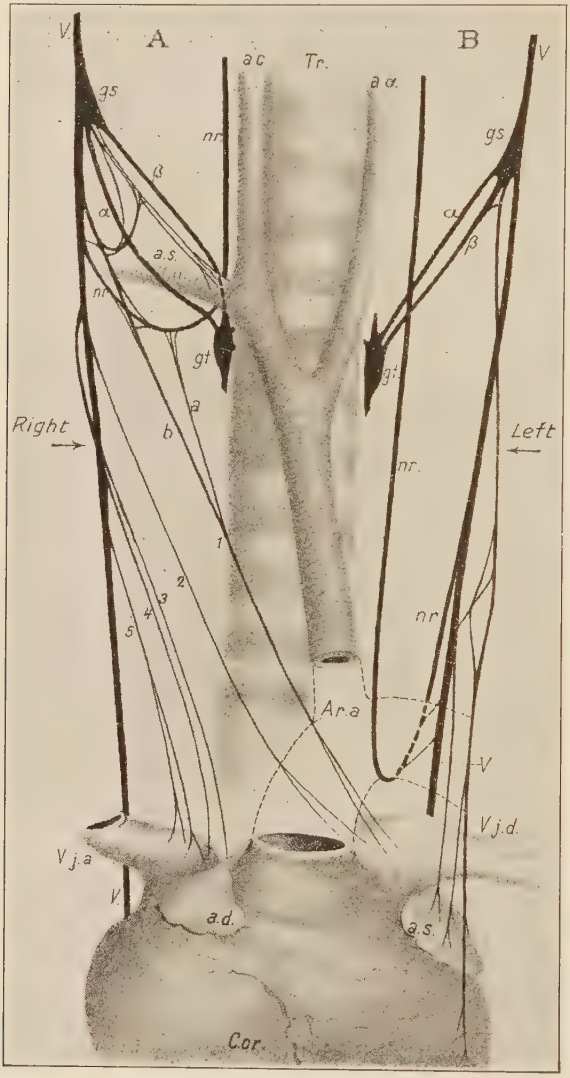


Fig. 33.—Nerve supply of the dog's heart. *V*, vagus nerve; *gs*, inferior cervica ganglion; *a*, *β*, annulus of Vieussens; *gt*, stellate (superior thoracic) ganglion; *nr* recurrent laryngeal nerve; 1 to 5, filaments of "cardiac plexus." (After Dogiel.) (Wiggers' Circulation in Health and Disease.)

These are: (*a*) Frequency of discharge of the pacemakers; (*b*) speed of conduction of the excitation wave; (*c*) irritability of the cardiac tissues; (*d*) force or amplitude of contraction of the muscle

fibers; (*c*) quickness of contraction of the fibers. (Engelmann designates the action of the extrinsic nerves on the first four of these properties as chronotropic, dromotropic, bathmotropic and inotropic effects, respectively.)

Action of the Cardiac Nerves on the Pacemakers.—The rate of the heart-beat depends on the frequency of discharge of the pacemakers, and it is upon this that the cardiac nerves exert their most conspicuous effect. When one or other of the vagus nerves is stimulated directly in an experimental animal the heart-rate is promptly slowed, or if the stimulation is strong enough the heart may come to rest in a state of complete relaxation. The latency of this action is brief; the effect appears in the very next contraction following the one in which stimulation is applied. Direct stimulation of the sympathetic cardiac fibers has precisely the opposite effect, quickening the heart-rate. In this action the latency is considerably longer, several beats occurring before quickening is seen.

There is abundant evidence that these changes in rate depend primarily on effects wrought directly on the pacemakers. One item is that the hearts of many kinds of mammals cannot be held stationary for more than a few seconds even by strongest possible stimulation of the vagus nerves. They soon "break through" the inhibition, resuming beating at a slower rhythm than normal. The explanation is that the inhibition prevents the nodal tissue from discharging excitations at the usual regular intervals, but does not affect the development in the other cardiac tissues of their inherent rhythmic property. This property accordingly comes into action and beating is resumed. In some kinds of animals, notably turtles, prolonged standstill can be maintained by continuous vagus stimulation. This is accounted for by the observation that in turtles, and presumably in the other species in which standstill can be maintained, the inherent rhythmic property of the contractile tissues is feebly developed at best, and under the conditions prevailing during vagus stimulation fails to become effective in initiating an independent rhythm.

Action of the Cardiac Nerves on Conduction of the Excitation Wave.—A frequent accompaniment of vagus stimulation, when so adjusted that only slowing and not complete stoppage occurs, is a tendency for the ventricles to lag further behind the atria than they do normally. This signifies a slowing of the conduction along the His-Tawara bundle. The neurons that cause this action appear to be distinct from those that bring about slowing of rate by depressing the nodal tissues. It is sometimes the case that the latter neurons are largely confined to the right vagus and the former to the left (Fig. 30). In an experimental animal in which this arrangement is present the left vagus can be stimulated strongly, with slight tendency to cut down the rate of beat, but with maximal influence on

the speed of conduction of the excitation wave. As a result of the slowing of conduction without changing the frequency A–V heart-block may be induced.

The augmentor (sympathetic) nerves (at least the one on the left side) contain neurons which act on the A–V node in such a way as to cause the ventricle to beat more nearly synchronously with the atria than they do normally. So far as the mechanical action of the heart is concerned, the effect is precisely opposite to the slowing of conduction by vagus action just described. The explanation usually offered is not, however, in terms of hastened conduction, but of a heightening of the pacemaker action of the A–V mode.

Action of the Cardiac Nerves on Irritability of Cardiac Tissue.—When a heart is subjected for a considerable period to a rapid succession of inhibitory stimuli through the vagus nerves the atria become less excitable than normal to such artificial stimuli as electric shocks. No similar effect has been seen on the ventricles.

Action of the Cardiac Nerves on the Force of Contraction.—Stimulation of the vagus ordinarily cuts down the amplitude of contraction of the atrial fibers. This action is not shared by the ventricles. On the contrary, these, on account of their slower rate, usually beat more forcibly under vagus stimulation than they do normally. When the sympathetic cardiac fibers are stimulated (particularly on the left side) the amplitude of both atria and ventricles is improved. This implies a distribution of sympathetic neurons to ventricular tissue, in contrast to the distribution of parasympathetic (vagus) neurons, none of which appear to extend beyond the atria.

Action of the Cardiac Neurons on the Quickness of Contraction.—Stimulation of the sympathetic cardiac fibers is followed by a quickening of the contractions of the ventricles (Wiggers and Katz). This action is important to the successful working of the heart pump at high frequency, for if the contractions were to take as long at a heart-rate of 150 to 160 per minute as at a rate of 60 to 70 the increased rate would have to be obtained altogether by shortening the time of relaxation between contractions (page 312). Since the heart is a reciprocating pump, it must fill while in relaxation in order to have blood to pump while contracting. Obviously cutting down the period of relaxation too much would nullify the advantage of increased rate. The quickening of the contraction tends to obviate this evil.

Theories of Inhibition and Augmentation.—Just how the inhibitory and augmentor effects are produced is not known, although much study has been devoted to the problem. The most promising lead at present, in respect to inhibition, is perhaps the one which assigns to the inhibitory nerves the function of setting free some chemical

substance that opposes the discharge of the pacemakers, slows down conduction in the His-Tawara system and lessens the excitability and amplitude of contraction of the atrial fibers. Howell pointed out in 1906 that potassium salts in excess in the cell environment have substantially the above effects, and later submitted evidence (Howell and Duke) that the concentration of diffusible potassium salts increases in the heart in connection with vagus inhibition. Other workers (Loewi; Brinkman and Van Dam) corroborate the view that inhibition is due to the release of a chemical substance, but think that some organic compound is the agent, rather than a salt of potassium.

The action of the augmentors, which is to increase the frequency of discharge of the pacemakers, improve the amplitude of contraction of both atrial and ventricular fibers, and quicken the contractions of the ventricle, has usually been explained by considering the sympathetic neurons equivalent to the ordinary motor neurons of skeletal muscle, *i. e.*, able to cause an upset of equilibrium within the tissue, with consequent excitation. This may account for the increase in frequency of discharge of the pacemakers. It does not explain either the improvement in amplitude or the quickening of contraction. To account for these, particularly if we accept the usual assumption that cardiac muscle function is essentially similar chemically and physico-chemically to that of skeletal muscle (page 83), a more deep-seated action is necessary. Here again, the obvious suggestion is that the augmentor excitations set free some chemical substance whose presence within the cells or in their environment favors more extensive and more rapid contractile processes than occur when the substances are wanting.

FUNCTIONS OF THE CARDIAC CENTERS.

In the last few paragraphs we have considered how the heart is affected by nerve impulses that reach it over the inhibitory and augmentor pathways. We have now to turn to a study of the cardiac centers (page 299) from which these pathways extend. It is in the centers that the streams of inhibitory and augmentor impulses are set in motion. The basic function of these impulse streams, and therefore of the centers which generate them, is to adjust the activity of the heart to the metabolic requirements of the body. Insight into the mechanism of this adjustment is to be had through a study of the centers.

Centers in "Tonic" Activity.—The evidence indicates that both the inhibitory and the augmentor center are normally in continuous (so-called "tonic") activity, discharging streams of impulses constantly to the heart. These constant impulse streams are of moderate intensity, much below the utmost the centers are capable

of generating. Proof of continuous tonic activity on the part of the cardio-inhibitory center is easy to obtain. Cutting one vagus in an experimental animal is usually followed at once by some quickening of rate. When both are cut considerable quickening is always seen, unless for some reason the heart was already at its maximum. Similar proof for tonic activity on the part of the augmentor center is not so simple experimentally for anatomical reasons, yet when all augmentor paths are severed the heart-rate decreases, provided it was not extremely slow before.

The centers are thought to be kept in their state of tonic activity mainly by virtue of constant streams of nervous impulses impinging upon them. Through the medulla, in which both centers are believed to lie, pass all impulses that move from the spinal cord to the brain, or from the brain to the spinal cord, as well as many impulses passing to or from organs within the head. These make up, as a whole, a continuous impulse stream. The neurons of the medulla are mainly of the internuncial type (page 104), with many collaterals, and it seems reasonable to suppose that some of these collaterals communicate with the cardiac centers. A mechanism for the tonic activity of the centers can thus be pictured in terms of the known facts of nervous functioning (page 120). To some extent the chemical condition of the blood circulating through the centers may contribute to their tonic activity. Thus, there is evidence that asphyxia of the inhibitory center in the early stages causes it to discharge actively (page 378). On the whole, however, this influence is thought to be subordinate to the nervous factors.

Heart-beat a Balance of Opposing Influences.—If the theories of inhibition and augmentation given above (page 302) are sound the view that both centers are continuously discharging impulse streams upon the heart means that one set of chemical substances favoring activity and another set opposing it are continuously being set free within the organ. In any event influences favorable to and opposed to activity are present simultaneously. The actual character of the beat, in other words, the frequency of discharge of the pacemakers and the amplitude and quickness of contraction, depends on the balance between these opposing substances or influences. The quantity of substance, or intensity of influence, depends, in turn, on the level of activity of the center through whose discharges it is set free. The fundamental tone of both cardiac centers is attributed to the general flow of impulse streams through the medulla. *Changes in level* of activity of the centers, on the other hand, are due chiefly to specific effects of impulse streams from particular sources. The most important of these are outlined in subsequent paragraphs. The interpretation of observed changes in heart-rate is complicated by the fact that increase may be due either to a cutting down of inhibitory influence or a height-

ening of augmentor influence, and decrease either to a heightening of inhibitory influence or a cutting down of augmentor. The interpretation is helped by recalling the fact already pointed out (page 301) that effects due to action of the inhibitory mechanism are very prompt in showing themselves, while effects wrought through the augmentor mechanism develop more slowly.

Activity of the Cardiac Centers in Relation to the Level of Basic Metabolism.—We have seen that the heart-rate is an important element in determining circulation volume (page 283), and that this, in turn, is a significant factor in maintaining metabolism. We naturally inquire how the metabolic condition of the body makes itself felt in the cardiac centers in such a way that their discharges become more predominantly inhibitory as metabolism is low and less inhibitory or more augmentor as metabolism mounts. So far as the general level of metabolism is concerned, we know that there is a fairly close correspondence between heart-rate and basic metabolic activity per unit of mass, although we do not know how the correspondence is achieved. The correspondence holds for different kinds of mammals. According to the rule that the basal metabolism in mammals is proportional to body surface (page 454) the metabolic activity per unit of mass is less in large animals than in small. In agreement with this is the fact that the heart-rate is also less in large animals than in small. Thus we have for the elephant, 25 to 28; for the horse, 36 to 50; for the dog, 100 to 120; for the rabbit, 150; for the mouse, 700. There is a similar agreement between heart-rate and size in human beings, as appears when different ages are compared. On the average, the new-born infant has a heart-rate around 140. This sinks during early childhood to 100, in the young adult to 75, in the aged to 70 and in extreme age, when bodily shrinkage occurs, rises again to 75 to 80.

Activity of the Cardiac Centers in Relation to Acute Changes in Metabolism.—One of the most familiar phenomena in physiology is the increase in heart-rate that accompanies muscular exercise. This is an adjustment of the heart's activity to an acute change in bodily metabolism. The adjustment is both prompt and delicate. So slight a movement as that of tapping a telegraph key is followed immediately by a demonstrable acceleration of the heart (Bowen). The response is so prompt that it can only be explained as due to a decrease in the activity of the cardio-inhibitory center, with a resultant decrease in the flow of inhibitory impulses. It is assumed that the stream of volitional or reflex nerve impulses, by which the muscular activity is aroused, impinges upon the inhibitory center through collaterals (page 304). The effect is to depress the center so that its discharges are less than before. There is sufficient warrant in nerve physiology for this conception of depression of a center by a stream of nerve impulses (page 730).

If the muscular exercise is more than momentary the augmentor center is aroused to increased activity also; presumably by the same impulse stream that is depressant to the inhibitory center. There is positive evidence that in severe exertion, in which two to three times the resting heart-rate occurs, there is not only a marked reduction in activity of the inhibitory center, but also greatly increased activity of the augmentor center. The evidence is found in the behavior of the heart immediately upon cessation of the exercise. What happens is a sharp drop in rate from the maximum of 150 to 180 to about 100 to 120, and then a gradual return to normal. The first sharp drop can hardly mean anything else than a resumption of the usual stream of inhibitory impulses from the cardio-inhibitory center, temporarily reduced or suspended through the depressing influences set in play by the exertion. The fact that the sharp drop in rate does not extend all the way to the preëxercise level, but only to a new higher level, from which subsidence is gradual, is evidence that the augmentor center has taken on an increased tonic activity, from which it returns gradually to its usual base line. Further evidence to the latter effect is given by the *quickening of individual ventricular contractions* in exercise, a quickening that is brought about only by augmentor stimulation so far as known (page 302).

In addition to effects on the cardiac centers due to streams of nerve impulses as described above, there appear also to be influences set up during exercise by chemical changes in the blood. There is always an increase in the amount of carbon dioxide in transit (page 233), and if the exercise is more than moderate an out-pouring of sodium lactate as well (page 234). The indication is that these act chiefly on the augmentor center, and perhaps explain why the return of the heart-rate to normal is gradual after the quick first drop described above. It is noteworthy that in trained athletes the heart is less accelerated during exercise and returns to normal more quickly afterward than in untrained persons. It is also well known that in trained athletes there is less out-pouring of lactates than in persons that are untrained.

After meals there is usually an augmented heart-beat. This is explained as due to reflexes set up from the alimentary tract and playing upon the cardiac centers. The heart-rate is also affected by mental activity. It is difficult for one to make a typical count of his own pulse because the attention necessary for counting brings about acceleration. The mechanism is thought to be an "irradiation" of nervous discharges from the active cerebrum down to the cardiac centers in the medulla. These are both examples of adjustment of heart-rate to acute changes in metabolism.

Activity of the Cardiac Centers in Relation to Blood-pressure.— *The Depressor Nerve.*—The blood in the arteries is under considerable

pressure (page 325). This pressure distends the arteries, the distention being obviously greater the higher the pressure. Receptors exist in the walls of the arch of the aorta, and perhaps in the walls of the coronary arteries as well, that are stimulated by distention. The sensory neurons from these receptors make up a nerve trunk that is separate in rabbits and some cats; bound up with the vagus in dogs and other mammals. (There is a separate nerve trunk in man thought to contain the corresponding fibers.) Where the trunk is separate it is known as the *depressor* nerve. Afferent impulses entering the central nervous system by way of this trunk or by way of corresponding neurons in animals in which the trunk is not separate, play upon several centers (page 335), among them the inhibitory center. There is reason to think that the impulse stream from this source may be a chief factor in maintaining the center in tonic activity (Einthoven). A marked decrease in arterial pressure as in traumatic shock (page 350) is attended in its early stages, before the nutrition of the centers has suffered, by a marked increase in heart-rate. The suggestion is that the lessening of distention in the aorta cuts down the volume of impulses passing up the depressor nerve. The resultant lowering of tone in the inhibitory center results in an increased heart-rate. Whenever the aortic pressure rises much above normal the stream of impulses to the inhibitory center is increased, the center becomes more active and the heart is slowed. The slowing tends to prevent further rise in pressure. Thus the afferent path from the heart and aorta to the inhibitory center has a protective function in addition to its tone-maintaining function.

Activity of the Cardiac Centers in Relation to Affective States.—The fact that the heart is innervated through the autonomic system presupposes the occurrence of effects due to emotions (page 735). The existence of these effects is too well known to call for comment. It is interesting, however, that the reactions of the heart to affective states enter so vividly into consciousness that the organ has and always has had a very large and wholly undeserved place in the literature of emotion.

Agencies that Affect Cardiac Activity Directly.—Various agencies that may reach the heart in the blood stream are capable of altering its beat directly. Changes in blood temperature causes changes in heart-rate, in substantially a linear relation (Newell Martin). This is in general accord with the effect of temperature on metabolism (page 156). In cold-blooded animals, and in mammals in hibernation, the effect is seen strikingly. It shows to some extent in the rapid heart of fever patients. In general, however, the temperature of mammals is too uniform for much change in rate due to temperature to show itself. Adrenin is a direct stimulant of tissues that receive sympathetic innervation, and as already

pointed out (page 202) augments the heart. In addition to increasing the rate adrenin quickens the ventricular contractions, as is to be expected (page 302), since it has the same effects as sympathetic nerve stimulation. Various drugs act directly on the heart. For an account of their action works on pharmacology should be consulted.

Summary.

The most significant data on the circulation are those on the quantity of blood delivered per unit of time. These data are significant because they express the extent to which the circulation is able to maintain metabolism. The quantity per minute is designated *unit circulation*. Figures obtained by the ethyl iodide method give for normal man at rest an average unit circulation of about 100 ml. per kilo body weight.

Determinations of unit circulation through individual capillary areas are possible in man only to a very limited extent. In experimental animals they have been made extensively. The instrument most used is the stromuhr of Ludwig, or a modification thereof.

Other circulatory data of importance are those on capillary pressure. These are significant because capillary pressure is a determining factor in filtration of blood plasma, in the action of the kidney glomeruli and in the action of gland cells in general.

The subdivisions of the circulatory apparatus are: (*a*) The *heart*, a reciprocating pump; (*b*) the elastic *arteries*, narrowing individually but widening in total cross-section as they ramify throughout the body; (*c*) the *arterioles*, minute tubes offering high resistance to the flow of blood through them, and subject to neuromuscular control of caliber; (*d*) the *capillaries*, differing from the arterioles in permitting interchanges of material through their walls; subject to control of caliber both through the nervous system and through chemical agencies in the blood; (in skeletal muscles and in some other tissues, probably fewer than one in ten are open simultaneously during rest); (*e*) the *venules*, differing from the capillaries chiefly in offering little or no possibility of interchanges of material through their walls, except possibly in the skin; (*f*) the *veins*, distensible tubes that converge upon the heart; the presence of valves prevents the backward flow of blood.

The *heart* is a double pump, each unit consisting of an *atrium* and a *ventricle*. The arrangement of muscular elements is such that both atria beat together, and also both ventricles.

The most rhythmic portions of the heart act as pacemakers in initiating the heart-beat. There are two pacemakers, the *sino-atrial* (*S–A*) *node* and the *atrio-ventricular* (*A–V*) *node*. The *A–V* node merges into the His-Tawara conducting system.

The normal heart-beat is initiated in the *S-A* node and spreads thence over the heart, passing to the ventricles by way of the *A-V* node and the His-Tawara system. There is a brief delay at the *A–V* node.

The nodal tissue owes its position as pacemaker to the fact that its *refractory period* is shorter than that of the other cardiac tissues.

Extra stimuli sent into the ventricles during their relative refractory phase may, if strong enough, arouse *premature* contractions (extrasystoles). A premature contraction is usually followed by a *compensatory pause.*

When the refractory phase is shortened abnormally in atrial tissue closed rings of excitation may be established around which the excitation waves travel indefinitely, giving off excitations to the other atrial fibers. If the resulting beats are coördinated the condition is known as atrial "flutter;" if incoördinated, as "fibrillation." Similar phenomena are theoretically possible in the ventricles.

In *heart-block* the conducting paths of the heart are interrupted, partially or completely. The chambers beyond the point of interruption fail to receive some or all of the excitation waves sent out from the pacemakers. The result is more or less incoördinated beating.

The lowering of potential accompanying excitation of tissues is sufficiently pronounced in the mammalian heart to cause potential variations of the body as a whole, synchronous with those of the heart. Photographic records of these potential changes of the body, as registered by the string galvanometer, are called *electrocardiograms.*

The autonomic innervation of the heart consists of two *centers* in the medulla, *inhibitory* and *augmentor*, and a nerve path from each to the heart. The inhibitory path belongs to the parasympathetic system, and lies in the vagus nerves. The augmentor path belongs to the sympathetic system and reaches the heart in the cardiac plexus from the inferior cervical ganglia.

The action of the inhibitory nerves is to lessen the frequency of discharge of the pacemakers (if intense, to stop their discharge altogether), to slow conduction in the His-Tawara system, and to lessen the excitability and amplitude of contraction of the atrial fibers. The theory has been advanced that these effects are due to the liberation of some inhibitory chemical substance, which is set free by vagus stimulation.

The action of the augmentor nerves is to increase the frequency of discharge of the pacemakers, improve the amplitude of contraction of both atrial and ventricular fibers, and quicken the contractions of the ventricle.

The activity of the heart is adjusted to the metabolic requirements of the body through the functioning of the cardiac centers. Both

centers are in continuous *tonic* activity, being kept so mainly by the impingement upon them of nerve impulses passing through the medulla. It is possible that chemical substances in the blood contribute also to the maintenance of the tone of the centers.

Changes in heart-beat are due to changes in the level of activity of one or both centers. These changes in level of activity are due chiefly to specific stimulation of the centers from definite sources.

There is a fairly close correspondence between heart-rate and basic metabolism per unit of body mass. The correspondence holds for different species of mammals and for human beings of various sizes. How it is maintained is not known.

Muscular exercise is attended by a prompt augmentation of the heart-beat. This is due at first to a depression of the inhibitory center, presumably by impingement upon it of the nerve impulses by which the muscular activity is aroused. When the exercise is more than momentary the augmentor center becomes more active, primarily, it is thought, through the action of the same nerve impulses that depress the inhibitory center; secondarily, through an effect of the accumulated metabolites in the blood.

The heart is augmented after meals and during mental activity. In both cases, presumably, through the action of nerve impulses that pass from the active alimentary tract or active brain to the cardiac center.

Low arterial blood-pressure is accompanied by a rapid heart, high arterial pressure by a slow heart. The relationship depends on the functioning of the *depressor nerve*, an afferent nerve from the heart and aorta, which conveys impulses that excite the cardio-inhibitory center.

Various affective states are attended by changes in cardiac activity. These are particular results of the general out-pouring of nervous impulses over the autonomic system in time of emotion.

The heart-beat may be influenced directly by agencies brought to it in the blood stream. Among agencies showing this property are the temperature of the blood, adrenin and various drugs.

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CHAPTER XIX.

CIRCULATION: THE CARDIAC CYCLE; VENTRICULAR OUTPUT; CIRCULATION TIME; VELOCITY OF FLOW.

THE CARDIAC CYCLE.

The sequence of events in the heart from one discharge of the *S-A* node to the next makes up the *cardiac cycle*. Included in it are contractions and relaxations of the chambers, opening and closing of the heart valves, flow of blood into and through the heart, expulsion of blood from the heart into the arteries, and the

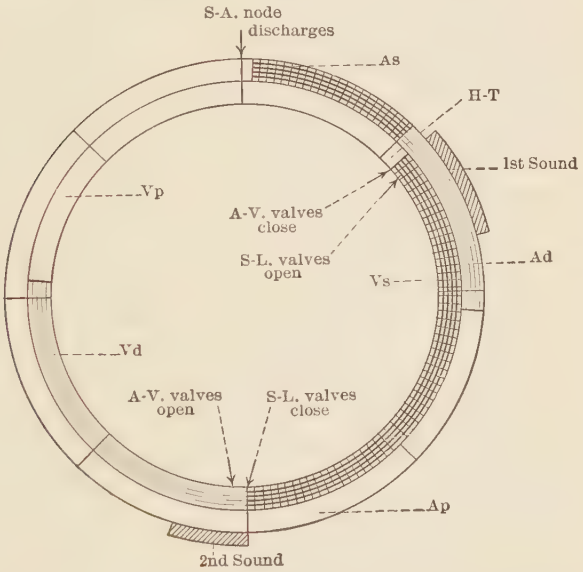

Fig. 34.—Diagram showing time relations of the cardiac cycle. Whole circle equals 0.8 second. *As*, *Ad* and *Ap*, atrial systole, diastole and diastasis respectively; *Vs*, *Vd* and *Vp*, ventricular systole, diastole and diastasis respectively. *H-T*, instant of passage of impulse over His-Tawara bundle. (Martin's Human Body, Henry Holt & Co., Publishers.)

heart sounds. The duration of a single cycle depends on the heart-rate. A convenient rate on which to base an account is 75 per minute, because at this rate the duration of a single cycle is exactly 0.8 second. In the accompany diagram (Fig. 34) this duration is assumed.

The period of contraction of a chamber of the heart is known as its *systole;* the period of relaxation is *diastole;* the period of quiet in the relaxed condition, when such a period occurs, is *diastasis.*

The Atria.—Systole, Diastole and Diastasis.—As the accompanying diagram shows, the first event following discharge of the sino-atrial node is atrial systole. This gets under way about 0.02 second after the discharge of the *S–A* node, and lasts about 0.08 to 0.10 second. The period of atrial diastole is a little longer, perhaps 0.10 to 0.12 second. Atrial diastasis continues from the end of atrial diastole to the beginning of the next atrial systole, a period of about 0.60 second. Since at ordinary heart-rates the period of recovery (diastole and diastasis together) in the atria is seven or eight times as long as the period of activity, and at the maximum rate the heart can assume more than three times as long, it is obvious that there is no likelihood of the atria becoming incapacitated by fatigue.

The Ventricles.—Systole, Diastole and Diastasis.—On account of the delay in conduction at the *A–V* node (page 293) ventricular systole does not ordinarily get under way until after atrial systole is completed. The exact interval varies with the heart-rate. At 75 per minute it is about 0.020 to 0.025 second. This "intersystolic" interval is important in the working of the heart-pump in that it allows time for the blood pumped from the atria into the ventricles in atrial systole to enter the ventricles without hindrance from the contractions of the latter.

There is a fairly definite relation between the length of the whole cardiac cycle and the duration of ventricular systole (page 302). At a heart-rate of 75 per minute the systole occupies 0.28 to 0.30 second (Wiggers and Clough). Diastole is a few hundredths of a second shorter, averaging 0.22 to 0.25 second. Diastasis completes the cycle; at a total duration of 0.8 second it would be about the same length as diastole.

When the heart is beating slowly (60 per minute) the duration of ventricular systole is more than 0.3 second. Diastole is also slightly longer than at 75 per minute. The greatest change is, however, in diastasis, which may be prolonged to nearly 0.5 second. At rapid heart-rates all the periods are shortened. When the rate goes above 100 per minute the systole takes less than 0.25 second; diastole may be cut down below 0.2 second. It is probable that at maximal heart-rates (160 to 180 per minute) there is almost no diastasis, atrial systole beginning while ventricular diastole is still in progress, and ventricular systole coming on practically at once upon the completion of diastole. The ventricles have proportionally much less time for recovery between contractions than the atria. They obviously recover completely between contractions, however, at least at ordinary heart-rates and in the long run what-

ever the rate for part of the time. Such relatively brief periods of maximal heart-rate, as may be experienced during intense exertion or in emotional excitement, are more than offset by the slow rate during sleep. As a rough expression of the relation of work to rest in the heart over a long period it is stated that the heart "enjoys an eight-hour day."

The Heart Valves.—These are membranous flaps so placed that when pushed into position they close the openings between atria and ventricles in the case of the *atrio-ventricular* valves (tricuspid, right heart; bicuspid or mitral, left heart), and between the ventricles and great arteries in the case of the *semilunar* valves (see diagram, page 291). There are smooth muscle fibers in the basal portions of the atrio-ventricular valves, but these do not appear to play any part in closing or opening the valves. The stout and inelastic *chordæ tendinæ* which pass from the ventricular surfaces of the mitral and tricuspid valves to the papillary muscles hold the valves in position when they are pressed shut, and prevent them from being turned inside out by the pressure which closes them. The action of the chordæ tendinæ is aided by the contractions of the papillary muscles. These are the tips of the muscle masses of which the walls of the ventricles are composed, and necessarily contract with every ventricular systole.

Each of the semilunar valves consists of three relatively deep pouches whose free edges meet and close the opening between artery and ventricle. Three tiny nodules, the corpora Arantii, one at the middle of the rim of each pouch, meet when the valve shuts and complete the closure. The semilunar pouches are deep enough so that they will not turn inside out when pressed shut, even though they are unprovided with chordæ tendinæ.

Action of the Heart Valves.—All the heart valves are pressure valves pure and simple. The atrio-ventricular valves are so placed that whenever the hydrostatic pressure in the atria is greater than in the ventricles the valves must be open; conversely, whenever the pressure in the ventricles is greater than in the atria the valves must be closed. Similarly, the semilunar valves are so placed that whenever the pressure in the ventricles is greater than in the great arteries the valves must be open, and whenever the pressure in the great arteries is greater than in the ventricles the valves must be closed. It follows that if one knows the relative blood-pressures in the various chambers and large vessels at any instant of the cardiac cycle one can deduce whether particular valves are open or shut at that instant. Conversely, if the position of the valves is known one can deduce the relative pressures in the chambers and large vessels.

Movement of Blood Through the Heart.—The *sources* of pressure in the heart are the muscular contractions of the atrial and ventricu-

lar walls. The same differences of pressure that operate the heart valves determine also the movement of blood; the *direction of movement* depends obviously on the working of the valves. It is convenient to analyze blood movement and valve action together on the basis of the pressures set up by the contractions of the cardiac walls. It is clear that blood will invariably flow from a point of higher pressure to a point of lower pressure. Since blood moves around the circulation from the left ventricle through arteries, arterioles, capillaries, venules and veins to the right atrium; thence to the right ventricle; from the right ventricle through the pul-

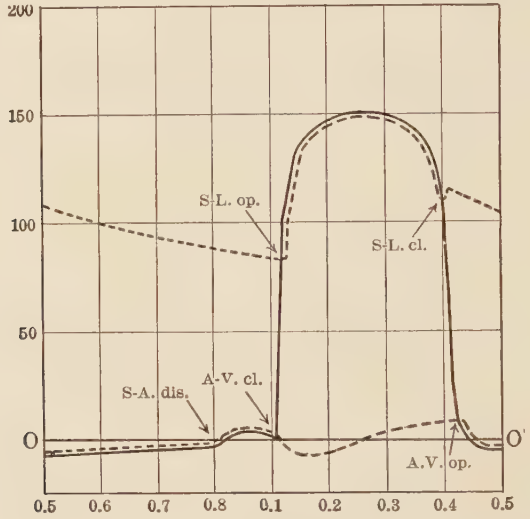

FIG. 35.—Pressure changes in atrium, ventricle and aorta during cycle of left heart. *O–O'*, atmospheric base line; figures on left vertical line represent pressures in mm. Hg.; figures at bottom represent time intervals in tenths of a second. The cycle is presumed to begin and end at 0.8, *i. e.*, at the instant of discharge of the *S–A* node. The solid line shows pressure changes in the ventricle, the lower dotted line in the atrium and the upper dotted line in the aorta. The action of the valves is indicated on the diagram: *op* = open; *cl* = close; *A–V* = atrio-ventricular; *S–L* = semilunar. (Martin's Human Body, Henry Holt & Co., Publishers.)

monary circuit to the left atrium, and so back to the starting-point in the left ventricle, pressure gradients corresponding to each stage of flow must be maintained. At the moment we are interested primarily in the pressure gradients which determine the movement of blood through the heart. Much that is brought out in this connection applies, however, to the movement of blood through the peripheral circulation, as will appear in later paragraphs (page 325).

Curves showing the course of the pressures in the left atrium, the left ventricle and the aorta during a single cardiac cycle are given in Fig. 35. (The pressures are stated in mm. Hg., the values signifying the height of the column of mercury that the given pressure

will sustain. Early determinations of blood-pressure were based on observations of the height to which a column of blood would rise in a tube connected with a bloodvessel of an experimental animal (Stephen Hales, 1733). This method does not lend itself to the taking of graphic records of blood-pressure, it depletes the animal of blood and is also unsatisfactory on account of clotting. To overcome these defects Poiseuille, and later Ludwig, introduced the mercury *manometer*, a glass U tube containing mercury, which is connected directly with a bloodvessel, and indicates the pressure by the difference in level of the mercury in the arms of the U. From the use of this instrument the practice has arisen of expressing blood-pressures in millimeters of mercury.) The pressure relationships in the right heart are similar to those in the left, although the maximum pressure in ventricle and artery are less than in the corresponding regions of the left heart.

Summary of Intracardiac Pressures, Blood Movements and Valve Action.—A summary of the relation between pressures, blood movements and valve action is as follows: In the later stage of diastasis of the whole heart both chambers are relaxed, pressure is low in the atria (1 to 13 mm. of water, page 344) and still lower in the ventricles; the atrio-ventricular (*A–V*) valves are accordingly open. Blood from the veins pours in a steady stream through the atria and the open *A–V* valves into the ventricles. It is interesting that Harvey, the discoverer of the circulation, made only one important error in his account of the action of the heart, written three hundred years ago. He thought that the ventricles remain empty during their diastole until filled by the systole of the atria. We now know that the *A–V* valves open early in ventricular diastole, and that blood then pours into the ventricles throughout the whole period of diastole and diastasis, so that under most conditions the ventricles are nearly full of blood when atrial systole begins. The pressure rises steadily in both atria and ventricles as blood pours into the them from the veins. The semilunar valves are closed because arterial pressure at this stage is much higher than ventricular.

Atrial systole raises the pressure in the atria, and since the *A–V* valves are open, giving free communication with the cavities of the ventricles, blood flows in an augmented stream into the latter. The curve of ventricular pressure follows closely that of atrial, although remaining slightly lower at each point. The augmented flow of blood sets up eddy currents in the ventricles, which act to float the flaps of the *A–V* valves into place. The result is that when atrial systole ends and ventricular systole begins the valve flaps are in position to snap shut the instant ventricular pressure rises above atrial, with practically no backward escape of blood. Although there are no valves between the atria and the great

veins no backward movement of blood is caused by atrial systole. The onward flow in the veins is checked more or less abruptly, giving rise to oscillations in pressure in the great veins that can be registered as the "venous pulse." (Registration is made from one of the large veins of the neck. The tracings have value in the interpretation of cardiac disorders of various kinds.)

Ventricular systole raises the pressure in the ventricles above that in the atria almost instantly, closing the *A–V* valves at once. The pressure continues to rise rapidly as the ventricular walls press upon the blood in the cavities. Presently it mounts above the pressure in the arteries, whereupon the *S–L* valves are pushed open and the blood in the ventricular cavities ejected into the arteries. The period of ejection extends from the opening of the *S–L* valves to the end of ventricular systole (about 0.27 to 0.29 second, page 312); the quantity of blood ejected is 90 to 125 ml. in an average sized man at rest (page 318). Ejection is exceedingly rapid at first and then slows down materially in the second half of systole. Throughout ventricular systole the curve of arterial pressure follows closely that of ventricular, as must be the case since the *S–L* valves are open, giving free communication between ventricles and arteries. The curve rises to a crest at about the middle of systole and falls off again, showing that the ventricles give their maximum effort in the early part of their contraction.

The instant the ventricles cease contracting and begin to relax, *i. e.*, as systole passes over into diastole, intraventricular pressure drops below arterial. A backward surge of blood from arteries to ventricles begins, but is interrupted practically at once by the snapping shut of the *S–L* valves. The backward flow of blood quickly fills the semilunar pouches and presses them into contact with each other, closing the valves. Enough momentum is gained by the backward surge, however, so that when the *S–L* valves close there is a rebound of pressure, which shows itself in the arterial curve as the "dicrotic" wave. The drop in arterial pressure due to the backward surge, before the valves close, is the "predicrotic" wave, also called sometimes the "dicrotic notch." Following the closing of the *S–L* valves arterial pressure declines steadily until the next ventricular systole raises it again (page 326).

Following the closing of the *S–L* valves at the beginning of ventricular diastole, intraventricular pressure falls swiftly as the ventricles continue to relax. Meanwhile the atria have been refilling with blood from the veins and the pressure in them has been rising. The result is that ventricular pressure quickly drops below atrial and the *A–V* valves are forced open. Following the opening of these valves there is a gush of blood into the ventricles from the distended atria and large veins. This gush takes only about a tenth

of a second, and coincides with the last period of ventricular diastole before diastasis begins. The higher the venous pressure the more blood enters the ventricles during this gush. When the heart is beating at maximum rate practically the only blood the ventricles get enters them during this period (page 312). It follows that a high venous pressure is essential to the maintenance of an adequate circulation whenever the heart is beating rapidly (page 344). During ventricular diastasis, when the rate is slow enough to permit one, blood continues to flow more or less sluggishly through the atria into the ventricles, as already pointed out (page 315).

The Heart Sounds.—Two main heart sounds occur in every cycle. They can be heard easily by laying the ear against the chest of a subject. (For convenience in listening the physician uses a stethoscope. The old form of this instrument is merely a small bell with ear tubes. It transmits the sounds without alteration. The Bowles stethoscope is constructed as a resonator. It accordingly magnifies the sounds, but some tones more than others, so that the sounds heard are not identical in quality with those produced.) The sounds are not musical notes but mixtures of irregular vibrations. The first sound is a booming noise lasting about 0.07 to 0.14 second. Its beginning coincides with the beginning of ventricular systole. Practically all observers agree that it is due to vibrations set up mainly by the contractions of the ventricular muscles, partly by the closing of the *A–V* valves. The second sound is shorter and somewhat higher in pitch than the first. Its duration is 0.04 to 0.10 second. It coincides with the closing of the *S–L* valves, thus marking the end of ventricular systole, and has been conclusively proved to be due to vibrations set up by the *S–L* valves as they snap shut. The character of the first and second sounds is suggested to some extent by the syllables, *lubb-dup*. In a considerable percentage of persons a faint third sound can be heard, provided the subject is lying on the left side and the stethoscope is over the apex. This sound is only about $_{2}\frac{1}{0}{}_{0}$ as loud as the first sound (Einthoven). It follows the second sound by about 0.13 second on the average, and, therefore, falls within the period of ventricular diastole. The most plausible explanation yet offered for it is that it is due to vibrations of the second sound delayed in transmission to the apex and so heard separately over that region (Einthoven). In various cardiac disorders the heart sounds are modified or attended by murmurs. These are of diagnostic importance. Their discussion falls outside the scope of this book.

Fig. 34, which is a graph of time, and Fig. 35, which is a graph of pressure, show between them the major events of the cardiac cycle. By comparing one with the other the time and pressure relationships can be readily coördinated.

VENTRICULAR OUTPUT.

By the ethyl iodide method (page 285) Henderson and Haggard have obtained apparently reliable figures for the quantity of blood ejected by the left heart (which, of course, equals the quantity ejected by the right heart) at each beat. They adopt the term "stroke index" to signify the quantity in milliliters per kilo body weight. The value of the index is obtained by dividing the "stroke volume," which is the total quantity ejected in one beat, by the body weight. They find the stroke index in normal persons sitting quietly to range from 1.3 to 1.8. The mean of these values corresponds, in a 70-kg. subject, to a stroke volume of 100 ml., and at a heart-rate of 70 to a unit circulation (page 283) of 7 liters. Changes in posture affect the stroke index; it increases in most subjects upon lying down (more than offsetting the decline in heart rate) and decreases on standing (often as much as one-third). In vigorous exercise the stroke index increases materially. The maximum thus far reported is 3.4. This corresponds to a stroke volume in a 70-kg. man of about 240 ml., and a unit circulation, assuming a heart-rate of 160, of 38.4 liters. Contrasting these figures of exercise with those of rest given just above, we note that a fivefold increase in circulation volume is apparently readily attainable (page 349).

Factors in Ventricular Output.—Venous Inflow.—It is obvious that the ventricular output tends to balance the venous inflow exactly, since the amount of blood the heart expels in systole is that which enters it during diastole and diastasis. (Residues of blood remaining in the ventricles at the end of systole may modify this relation for a beat or two, but not in the long run; next page.) When the stroke volume more than doubles, as in the illustration in the paragraph above, more than twice as much blood as before must enter at each beat. This increased intake often occurs in connection with an accelerated heart-rate, and so implies a much quicker movement of blood. The only factor that will cause blood to flow at an increased rate, the caliber of the vessels remaining unchanged, is a steeper pressure gradient, in other words, a greater difference between venous pressure and intraventricular pressure (at the beginning of diastole). Although the contrary was held for a long time, it appears to have been conclusively proved that the relaxing ventricles have no "suction" effect. Intraventricular pressure in them is merely that of the region as a whole. This region is the thorax, within which pressure is ordinarily le s than atmospheric by 4 to 6 mm. Hg. or 50 to 80 mm. H_2O (page 383). The pressure gradient is the difference between this figure and the pressure in the great veins. In the resting body this latter pressure is probably around 10 mm. H_2O (page 344), giving a gradient of

60 to 90 mm. H_2O. To provide for the greatly increased inflow in exercise venous pressure must obviously mount considerably. The conditions that bring about and control this increase, as well as the corresponding decrease when the change in output is in the reverse direction, are discussed in later paragraphs (page 349).

Distention in Diastasis.—A change in cardiac output always involves in the long run an equivalent change in intake, as pointed out on the last page. So far as individual beats are concerned, however, the equivalence does not always hold exactly because the heart may empty itself more completely at one beat than at another. There is direct evidence that in the normally beating heart one-half to one-fourth of the blood contained in the ventricles may, under certain conditions, remain unexpelled at the end of ventricular systole. This residue is unimportant, however, when we contrast the 240 ml. or so that the heart pumps per beat in vigorous exercise with the 90 to 120 that it pumps when the body is at rest. Obviously the ventricles have much more blood in them in diastasis when the output is high than when it is low, even after allowing for a more nearly complete emptying in the one case than in the other. This greater capacity is achieved by a greater yielding of the ventricular walls. A heart that is pumping 240 ml. is much more distended in diastole than one that is pumping only 100 ml. The distention is purely passive. The relaxed ventricle is soft and flabby, and yields without much resistance to the inrush of blood. Since the distended heart does not usually have more time in which to eject its greater quota of blood, but rather less, it must obviously exert greater force. One of the very interesting and important facts of cardiac physiology is that the more the ventricular muscle strands are distended (within reasonable limits, and *provided the heart is normal*) the more powerfully do they contract. We have no satisfactory explanation of why this is so. We only know it to be the fact.

Augmentation of force of beat by increased distention accounts also for the ability of the heart to eject as large quantities of blood against a high arterial resistance (page 325) as against a lower. If the resistance increases, as it may readily (page 333), the heart, which is beating with the degree of force suitable for overcoming the lower resistance, is unable to discharge as much blood against the increased resistance and so has a greater contained residue at the beginning of diastole. The venous inflow being as usual, the ventricular walls are distended more than before to accommodate both the inflow and the larger residue. They react to this greater distention by a more forcible contraction. Thus, in a few beats the degree of distention and the resulting force of contraction become adjusted to the new load, and as much blood is ejected per beat as before the resistance increased. Through this fundamental

relation between distention and force of contraction the heart's action is adjusted to its task, both in respect to amount of blood to be ejected per beat, and to the resistance to be overcome in ejecting it.

Work of the Heart.—Each ventricle of the heart expels at each beat a given mass of blood against a resistance which first rises and then falls (page 330), and imparts to it a velocity, high at the outset, and very rapidly declining thereafter to the end of systole. If the resistance and velocity were uniform the familiar formulæ for work (work = mass times height) and kinetic energy $\left(W = \frac{MV_2}{2g}\right)$ would be applicable. Then if the resistance encountered by the right heart and the velocity imparted to the blood in both right and left hearts in man could be actually determined instead of merely guessed at, an accurate computation of the work done by the human heart could be made. Under the conditions that exist the unknown factors are so numerous and the corrections to be applied to the above formulæ so complicated that only the roughest of estimates can be offered. These range in the hands of various authors from 150 to 300 gm. meters (1 to 2 foot pounds) of work per beat in the heart of the resting body. In maximal exertion the work per beat is three or four times as much as in rest. Reasonably accurate determinations of all the factors in experimental animals indicate that the mechanical work done by the heart accounts for something like 20 per cent of the total energy developed in it. This finding makes cardiac muscle substantially equal in mechanical efficiency to skeletal muscle (page 88).

CIRCULATION TIME.

If the stroke volume (output per beat) and the total quantity of blood in the body are known dividing the second figure by the first gives the number of beats required to move the equivalent of the whole mass of blood around the circulation. From the heart-rate the time taken in making this number of beats can be determined, and so the circulation time for the body as a whole estimated. This is the time for a complete round of both the systemic and pulmonary circuits. If we accept the figure 3500 ml. for the blood volume of a 70-kg. man (page 271), 100 ml. for the average stroke volume (page 318), and 70 for the heart-rate the circulation time works out at about thirty seconds (35 heart beats). This is obviously only an average figure. The circulation is made up of so many paths varying in length and resistance that the blood actually in the heart at any instant is not identical with that which left it thirty seconds before, but is a mixture of some that left longer ago and other that left only a few beats before.

Direct tests of the time required for a sample of blood to pass from any point back to the same point, or to some other selected point, are made by introducing an easily detectable substance into the blood and noting the time elapsing before it appears at the spot selected. Compounds like sodium or potassium ferrocyanide, which can easily be precipitated as Prussian blue, have been used for the purpose. In animals with semitranslucent vessels (albino rabbits) methylene blue, a harmless and quickly decolorized dye, serves well. Its great advantage is that blood need not be drawn at frequent intervals and tested for it, since it can be seen as a dark flash passing along the vessel. The method developed by Stewart of introducing salt solution into the circulation and testing for the time of its arrival by noting a change in electrical conductivity has given valuable information in experimental animals. Since all direct methods give the time for traversing the shortest possible path between the selected points, estimates of total circulation time based on them are generally somewhat shorter than estimates based on total blood volume and cardiac output. The earlier workers with the direct method suggested the generalization that in mammals 26 to 28 heart beats are required for a complete circuit, regardless of the size of the animal. This, applied to man gives an estimated circulation time of about twenty-three seconds, as compared with the estimate of thirty seconds by the method described in the preceding paragraph.

VELOCITY OF BLOOD FLOW.

The average linear velocity of the blood per unit of time in any vessel is equal to the volume passing through it in that time divided by the cross area of the vessel. In experimental animals measurements of volume flow in most of the larger vessels have been made with the aid of *stromuhrs* (page 286), and the velocity computed. Direct velocity determinations have also been made by means of an apparatus (the hemodromograph of Chauveau) in which a plate or needle is inserted in the vessel in the path of the blood in such a way that the pressure of the flowing blood will tend to deflect it, the degree of deflection being dependent on the velocity. Assuming the apparatus to have been properly calibrated, the velocity is determined directly by noting the degree of deflection. Data from these two methods indicate a velocity in the carotid artery of the dog and horse, for example, of 250 to 300 mm. per second.

In man the unit circulation, and hence the flow per second, can be determined by methods already described (page 283). For a 70-kg. man, according to figures quoted on page 285, the flow per second is about 120 ml. This is the volume which passes each

level of the circulation in the time stated; dividing it by the total cross area of that level, if the same is known, gives the mean velocity of the blood at that particular level. Conversely, if the mean velocity at any level is known the total cross area of that level can be readily calculated. The only levels at which the total cross area can be measured with any real accuracy are those in which all the blood is confined in one or two, or at the most a very few, channels. In effect the arteries and veins near the heart are the only portions of the circulation that fulfil the conditions. On the basis of measurements of these vessels the statement is made that the velocity in the human aorta is probably around 500 mm. per second, and in the great veins near the heart about one-half as much.

As the arterial system widens out (page 286), the mean velocity declines in proportion. By the time individual organs are reached the total stream bed has broadened out so extensively that the mean velocity is only a few millimeters per second. The maximum stream widening occurs in the capillaries. From estimates of the functioning capillary volume of the resting body an idea of the cross area of the capillary bed can be obtained. All that is necessary is to divide the estimated volume by the average capillary length, 0.5 mm. The table of blood distribution on page 273 estimates the total blood content of the small bloodvessels, exclusive of the pulmonary, at 2100 ml. Calculations based on Krogh's direct studies of capillaries (see Chapter XXI), indicate the systemic capillary volume to be at least 10 per cent of the total small-vessel volume (in the resting body). Assuming then a capillary volume of 210 ml. the cross area becomes 420,000 sq. mm. The volume flow of blood per second, stated above as about 120 ml., or 120,000 c.mm., divided by this cross area, gives a mean capillary velocity of approximately 0.30 mm. per second. It is important to note that any *increase* in capillary volume, other factors remaining constant, implies a corresponding *decrease* in capillary velocity. If the estimate as to functional capillary capacity is too low (page 289), the above calculation for mean velocity of capillary blood flow is correspondingly too high.

Beyond the capillaries the blood stream quickens again as the bed narrows, through the convergence of the veins. Comparisons of individual veins and arteries at various levels indicate that in general, the venous stream bed, level for level, is about twice as wide as the arterial. The velocity is accordingly about one-half as great in veins as in corresponding arteries.

The figures thus far given apply only to the resting body. Whenever activity occurs unit circulation goes up, increasing the velocity at all points proportionately. Changes in caliber of individual arterioles and venules (page 333), and opening out of capillaries

previously closed (page 289), usually occur also, bringing about marked changes in the relative velocities in different parts of the circulation.

Summary.

The cardiac cycle includes *systole*, *diastole* and *diastasis* of the atria, and a corresponding sequence in the ventricles. In a heart beating 75 times a minute atrial systole lasts 0.08 to 0.10 second, atrial diastole 0.10 to 0.12 second and atrial diastasis about 0.60 second. Corresponding figures for the ventricles are: Systole, 0.28 to 0.30 second; diastole, 0.22 to 0.25 second; diastasis, about 0.25 second. All the periods lengthen at slower rates and shorten at higher, although diastasis is affected most.

The heart valves are pressure valves pure and simple. Whenever the pressure in the atria is greater than in the ventricles the *atrio-ventricular* (*A-V*) valves must be open; whenever ventricular pressures exceed atrial the *A-V* valves must be shut. The *semilunar* (*S-L*) valves are open when ventricular pressures exceed arterial, and shut when arterial pressures exceed ventricular.

Blood tends to move always from points of higher to points of lower pressure. Contractions of the atrial and ventricular walls establish pressures which set the blood in motion, the direction being determined by the action of the heart valves. Details of intracardiac pressure, blood movement and valve action are given in graphs in the body of the text.

Two main *heart sounds* occur in every cycle. The first coincides with the beginning of ventricular systole; the second with the closing of the semilunar valves, thus marking the end of ventricular systole. A very faint third sound can be heard in some subjects in a certain bodily position. It follows the second sound by about 0.13 second.

The output of either ventricle per beat is known as the *stroke volume*. This figure divided by the body weight (kilos) gives the *stroke index*. The value of the latter in normal persons sitting quietly is given as 1.3 to 1.8 ml. In vigorous exercise the stroke index may rise as high as 3.4 ml.

Factors determining ventricular output are *venous pressure* (on which the inflow into the heart depends) and the force of ventricular contraction (determined by the *degree of distention* of the ventricular muscle strands).

Rough estimates of the *work done* by the human heart give 150 to 300 gm. meters per beat for the heart of the resting body. In maximal exertion the work is three or four times as much. Experiments on animals indicate that the mechanical efficiency of the heart is around 20 per cent.

Average circulation time (in fraction of a minute) is obtained by dividing the total quantity of blood in the body by the stroke volume and then dividing the quotient by the heart-rate per minute. Determinations can be made experimentally of the time required for blood to pass from one selected point to another by the *shortest path*. Estimates of total circulation time based on these direct determinations usually give somewhat smaller figures than by the method of calculation.

The *velocity of blood flow* is equal to the volume per unit of time divided by the cross area of the circulatory bed. In the human aorta the mean velocity is estimated at about 500 mm. per second. As the arterial system widens out toward the periphery the velocity falls off, reaching a minimum estimated at about 0.30 mm. per second in the capillaries. The narrowing of the venous system brings about a quickening of the blood flow again. On the whole the velocity in the veins is about one-half that in the arteries at corresponding distances from the heart.

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CHAPTER XX.

CIRCULATION: ARTERIAL PRESSURE; THE PULSE; THE VASOMOTOR MECHANISM.

ARTERIAL PRESSURE.

The arterial system (either systemic or pulmonary) consists of a set of branching elastic tubes terminating in innumerable microscopic outlets (page 287) which offer considerable resistance to the flow of blood through them. Let us assume a situation in which the arteries are empty of blood, the peripheral resistance has a constant value, and the left ventricle begins to pump blood into the main arterial system at a rate of 75 per minute and with a uniform stroke volume of 100 ml., giving a unit circulation (page 283) of 7500 ml. The first half dozen beats will fill the arteries with blood and stretch them slightly. (Estimates of the capacity of the undistended arterial tree do not exceed 500 ml.) The stretched arteries will react with an equivalent pressure on their contents. This is *arterial pressure*. As soon as any actual arterial pressure is established blood will begin to be forced through the microscopic outlets at a rate determined by the relation of the mean pressure to the peripheral resistance. At first this rate will be much below the rate of input from the heart, and so blood will accumulate in the arteries, stretching them more and more, and so raising mean arterial pressure to a higher and higher level. As the pressure rises blood is forced through the peripheral outlets faster and faster. As soon as the mean pressure becomes great enough so that the outflow equals the input, which in the situation assumed here is when 7500 ml. of blood are being forced out every minute, equilibrium is established and no further change in mean pressure will occur unless there is a change either in peripheral resistance or unit circulation. If either one increases while the other remains unchanged pressure will rise until equilibrium is reëstablished on a higher level. Conversely, a drop in either (the other not changing) will cause a fall in pressure to a new lower equilibrium level. Since increased arterial pressure implies greater stretching of the arterial walls, it follows that the higher the pressure the more blood will the arteries contain. (This is true for any one individual. Differences in elasticity, such as obtain in different people, will mean different quantities of blood for equal arterial pressures.) Conditions are so far from uniform in man that it is hard to make a statement as to

average mean arterial pressure. It is probable that 106 to 110 mm. Hg. is not far from the average.

Systolic and Diastolic Pressure.—At each ventricular systole the entire stroke volume of blood is suddenly injected into the arteries. The injection occurs mainly during the first half of systole (page 316), continuing more slowly to its end. During this time blood is escaping through the microscopic outlets as fast as the prevailing pressure can force it past the existing resistance. But the rate of escape is adjusted to the whole cardiac cycle and not to the period of systole, and so is necessarily considerably below the rate of systolic input. The resulting surplus of blood is accommodated by a further stretching of the arterial walls. The pressure thus set up is at its maximum when ventricular pressure is also at its maximum (Fig. 35, p. 314), at which point it is designated as *systolic* pressure. From the instant of closing of the semilunar valves, with consequent withdrawal of the support of the contracting ventricles, the blood in the arteries is subjected exclusively to the pressure of the stretched arterial walls. The force supplied by this pressure continues to drive blood through the outlets as fast as the resistance permits. The escape of blood, in turn, relieves the pressure, which accordingly falls continuously until interrupted by the next ventricular systole. The point of lowest pressure obviously occurs at the end of ventricular diastasis. It is designated *diastolic pressure*. If systolic pressure were maintained uniformly during half the cycle and diastolic pressure uniformly during the other half, a value midway between them would correspond to average or mean arterial pressure. As a matter of fact the mean pressure ordinarily lies somewhat below the middle point.

Pulse Pressure.—The *difference* between systolic and diastolic pressures is designated *pulse pressure*. Changes in mean arterial pressure due to increases or decreases either in pulse-rate or peripheral resistance do not result in marked alterations in pulse pressure since systolic and diastolic pressures tend to follow changes due to these factors by rising or falling nearly together (as a matter of fact, systolic pressure usually rises and falls somewhat more than diastolic, hence pulse pressure is usually greater at high arterial pressures than at low). *Increase in stroke volume* or *shortening of systole* raise pulse pressure by affecting the input of blood into the arteries more than the escape of blood from them, in other words, these factors influence systolic pressure more than diastolic. Conversely, lessening of stroke volume or lengthening of systole lowers pulse pressure.

The less elastic the arterial walls the greater the pulse pressure, other conditions remaining unchanged. Two factors interact to establish this relationship. In the first place, injection of a given quantity of blood into a less elastic system, from which the outflow

offers equally high resistance, necessarily requires greater force and hence sets up greater systolic pressure. In the second place the less elastic walls absorb less of the energy of the heart-beat during systole and hence have less to give out during diastole. Diastolic pressure, therefore, falls more rapidly and to a lower level than in arteries with more elastic walls. In human *arteriosclerosis* (lessened arterial elasticity) compensatory factors usually enter, hence pulse pressure is not ordinarily as much higher than normal as the state of the arteries would lead one to anticipate.

Particularly large pulse pressures are seen in cases of aortic insufficiency, in which the escape of blood back into the ventricles allows

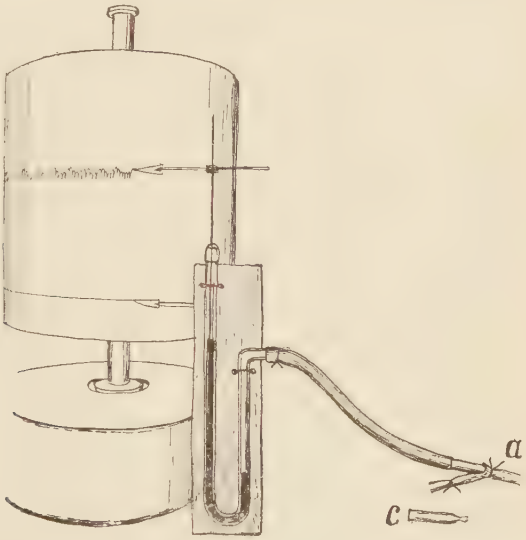

FIG. 36.—Mercury manometer connected for blood-pressure determination. *a*, artery of animal into which a cannula (shown separately at *c*) is inserted. (From Stiles: Human Physiology, W. B. Saunders Company, Publishers.)

diastolic pressure to fall inordinately, and the exceptionally vigorous contractions of the compensated heart raise systolic pressure to unusual heights.

Arterial Pressure Determinations in Lower Mammals.—Blood-pressure determinations in experimental animals are simple in theory, since all they demand is the insertion of a suitable pressure gauge into a convenient bloodvessel. In practice the mercury manometer as arranged for graphic recording by Ludwig (Fig. 36) is most commonly used. On account of the inertia of the mercury column this instrument does not follow accurately the rapid change of pressure from diastolic to systolic that accompanies each beat, a fact to be borne constantly in mind in using it. For determining mean pres-

sures and pulse-rate, and for following not too rapid changes in mean pressure it is, however, entirely adequate. Gauges of small inertia must be used if the changes in pressure in individual cardiac cycles are to be followed. Several such exist. For an account of them the reader is referred to larger works on the circulation.

Determinations of Systolic and Diastolic Pressure in Man.—Since gauges obviously cannot be introduced directly into the bloodvessels of human beings, some less direct method of determining arterial pressure must be used. The principle on which practically all serviceable instruments for the purpose (sphygmomanometers) are based is that of applying compression to a segment of the upper arm in amount just sufficient to balance the systolic or diastolic pressure in the part of the brachial artery within the segment. Compression is applied by means of an arm piece, which consists of a bag of fairly heavy rubber, at least 12 cm. wide, surrounded by an unyielding cuff, usually made of leather. The cuff with the rubber bag underneath it is strapped around the upper arm, and the bag is inflated by means of an air pump (a syringe bulb answers well). A side tube from the bag leads to a gauge so that the compression applied can be noted. It is necessary to have in addition some means of determining when the pressure applied just balances the systolic or diastolic pressure one is seeking to determine. A means that serves well in practice, and is also fairly simple in theory, is the "*auscultatory*" method (Fig. 37). In using this method the pressure in the arm bag is raised above systolic, so that the artery is fully compressed. The pressure is then allowed to fall gradually, by means of a tiny leak in the system. The bell of a stethoscope is placed over the brachial artery in the intercubital fossa, and when the pressure in the arm bag just balances systolic pressure, a faint sound begins to be heard. The sound is attributed to vibrations set up by blood that succeeds in passing the cuff into the empty artery beyond, and begins with the first blood that passes, *i. e.*, the instant the compression sinks below the highest (systolic) pressure within the artery.

To determine diastolic pressure the compression is allowed to go on sinking. The sound heard in the stethoscope changes somewhat in character and becomes louder and louder, and then is suddenly muffled. The pressure at which transition occurs from a rather loud clear sound to a muffled sound is accepted by most investigators as coinciding with diastolic pressure. The theoretical explanation is based on the principle that so long as compression is above diastolic pressure the artery will be squeezed shut during part of every cycle and open during another part. In every cycle there will thus be a sudden burst of blood into an artery in which no movement is occurring, giving rise to a "water hammer" effect with its accompanying sound. As compression sinks the phase of

closure becomes shorter and shorter and the burst of blood more and more energetic, making the sound louder and louder. At the instant compression sinks below diastolic pressure, however, the phase of closure disappears, there is no longer complete stoppage of motion in the artery below the cuff, and the "water hammer" action is greatly dulled. Other criteria besides the auscultatory have been devised for both systolic and diastolic pressure, and are in use. Lack of space forbids their discussion here.

Normal and Abnormal Pressures.—The normal range of systolic pressures in young adult males is given as 100 to 135 mm. Hg., averaging about 125. After middle life pressures 10 mm. Hg. higher may be considered normal. In women the figures range about 10 mm. Hg. lower at all ages. Diastolic pressures range

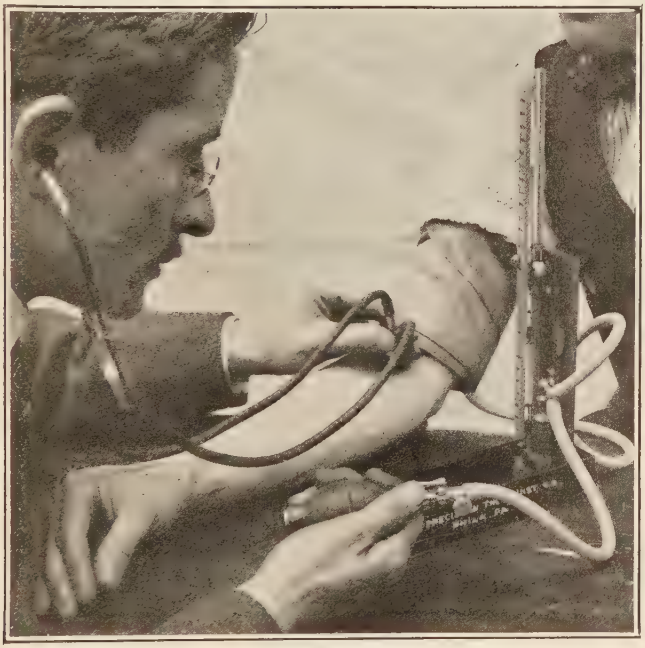

FIG. 37.—Auscultatory method of determining arterial pressure. A Nicholson one-limb mercury manometer is here used as the pressure gauge. (After Norris.) (Wiggers' Circulation in Health and Disease.)

normally between 70 and 100 mm. Hg. When pressures higher than normal occur the condition is described clinically as *hypertension;* when lower than normal the condition is *hypotension.* The great significance attached to blood-pressure determinations is due to the fact that in the normal individual the mechanisms of compensation (see below) operate effectively and hold the blood-pressure

very constantly within the normal range. Any persistent departure from the normal range is indicative of a failure of compensation, and hence of an abnormal situation demanding attention and perhaps treatment.

Compensatory Regulation of Blood-pressure.—A change in peripheral resistance must bring about a change in arterial pressure (page 325) unless counteracted by an equivalent change in unit circulation in the opposite direction, and *vice versa*. The mechanisms for controlling unit circulation have already been discussed. They consist of mechanisms for controlling stroke volume (page 318) and heart-rate (page 299). The latter is the one ordinarily invoked to compensate for a change in peripheral resistance. The compensation is effected by reflex slowing of the heart when pressure rises and reflex quickening when it falls (page 307). The mechanisms for adjusting peripheral resistance to compensate for changes in unit circulation operate through regulation of the caliber of the arterioles chiefly; secondarily through regulation of the caliber of capillaries and venules. Detailed discussion of these mechanisms is given in later paragraphs (pages 333, 341).

THE PULSE.

The sudden injection of blood into the large arteries during systole acts in part to push the mass already present forward bodily and in part to distend the elastic arterial walls, bringing about the change from diastolic to systolic pressure (page 326). The wave of distention, which is the *pulse*, spreads from the heart toward the periphery with a velocity inversely proportional to the elasticity of the arteries, hence the more the vessels yield the slower the pulse advances. Normally the rate is about 7 to 8 meters a second. This velocity is high enough so that by the time the systole is over, and the injection of blood into the aorta ceases, the front of the wave has passed beyond the smallest arteries, even in a very tall man. The distention is greatest next to the heart and becomes steadily smaller and smaller as the pulse wave advances (Fig. 38), fading out altogether as the capillaries are reached. The decline in size represents the steady conversion of part of the kinetic energy of the heart-beat into the potential energy of stretched arterial walls, this potential energy becoming kinetic again to keep the blood moving forward during diastole.

Contour at the End of Systole.—If we represent the arterial system by a single elastic tube of uniform caliber, from which outflow is just as difficult as in the branching system actually existing, we can picture the contour at the end of systole something as indicated in Fig. 39 (the effect of the dicrotic wave is omitted). The outer dotted lines (*dd'*) represent the maximum distention at each point

along the tube as the peak of the pulse wave advances. Successive points on the solid contour lines (*cc'*) represent the degree to which, at the end of systole, the artery has contracted from the position of maximal distention which it took when the peak of the pulse wave

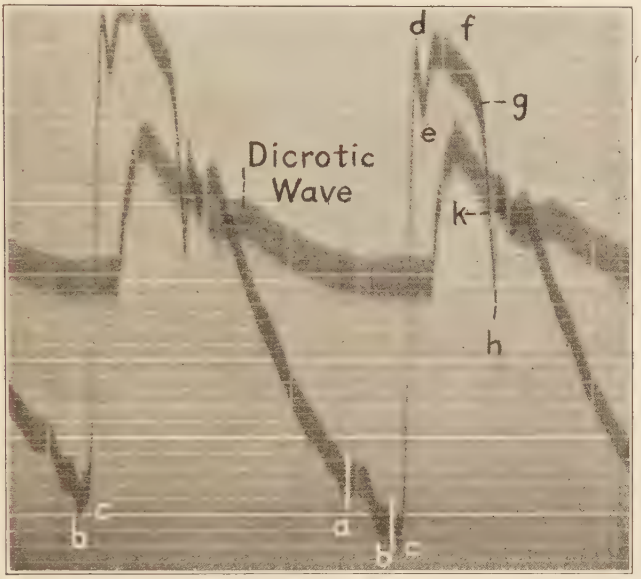

FIG. 38.—Great pulse distention in an artery near the heart (subclavian) contrasted with much smaller distention in a more distant artery (radial). (Wiggers' Circulation in Health and Disease.)

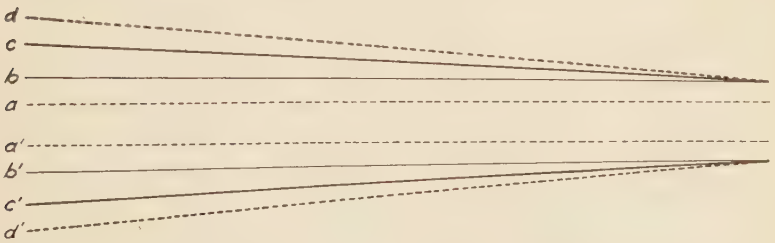

FIG. 39.—Contour of elastic tube at end of systole. Lines *aa'* indicate caliber of tube when undistended; lines *bb'* indicate positions of successive points of the tube under diastolic tension; lines *cc'* indicate contour at end of systole; lines *dd'* indicate successive points of maximal (systolic) distention.

passed over it. The inner solid lines (*bb'*) represent the position of diastolic tension which each point in the tube is due to reach just before the next pulse wave arrives. All the ventricular output except that portion which finds escape through the capillary outlets during systole is accommodated in the spaces between the

contour lines and the inner solid lines. The mass movement of blood during systole is forward and sidewise to the exact extent needed for filling up the contour as the pulse wave advances, plus the forward movement due to the escape of part of the ventricular output through the capillaries during the same period. The linear velocity during systole is considerably greater than during diastole, since in systole blood must be propelled fast enough to fill the increasing contour of the distended artery, as well as to provide for the continuous outflow.

The arterial system is actually not a single tube of uniform caliber, but a continuously subdividing system in which the number of vessels and the total caliber become greater and greater, while the caliber of individual vessels becomes smaller and smaller. On account of this subdivision the pulse distention as it advances is distributed to a constantly increasing arterial surface. The elastic area available for absorbing kinetic energy becomes greater and greater, and so the pulse decreases in size faster than it would in a single tube of uniform caliber. Except for this difference, the description of contour given for a single tube applies to the arterial system.

An increase in velocity of flow occurs during systole as far out in the system as there is any pulse, since it is by means of such an increase that the blood which actually distends the arteries is pushed into place (page 330). The velocity becomes uniform as soon as the pulse wave disappears, *i. e.*, at the entrance to the capillaries. An exception to this statement appears in regions where for some reason marked dilation of the microscopic vessels occurs with correspondingly marked lessening of resistance to outflow. Maintenance of a uniform outflow through the capillaries depends on the conversion of part of the kinetic energy of the heart-beat into potential by stretching the arterial wall (page 325). The condition for this conversion is marked resistance to outflow. In the absence of such resistance not sufficient stretching occurs to maintain steady pressure throughout diastole, and the capillary flow becomes intermittent.

Pulse Determinations.—The pulse can be felt with the finger tips in any fairly large superficial artery. The radial at the wrist is usually used for the purpose. The experienced physician gains much information from "feeling the pulse." Not only is the heart-rate thus measured, but qualitative estimates of arterial pressure, and in some cases of the state of the heart valves, are also possible. Various instruments have been devised for obtaining graphic records of the pulse. They are known as *sphygmographs*. In the common types a button is pressed against the radial artery at the wrist by a delicate spring, and the excursions of the button due to the pulse movements transmitted to a recording surface by a

system of levers. In more refined instruments the excursions are recorded photographically on moving films. Tracings from a sphygmograph of the latter type are reproduced in Fig. 38. It is necessary to guard against errors due to inertia of the lever system in interpreting most kinds of sphygmograph tracings. The curves show first the rapid distention of the artery as the peak of the pulse wave passes under the button of the instrument, and then the return to diastolic position, with the rebound, which is the dicrotic wave.

FUNCTION OF THE ARTERIOLES.

The existence of a high resistance to outflow from the arteries has been emphasized as the reason why the heart has to maintain a high arterial pressure. The resistance is mainly in the microscopic arteriole–capillary–venule sequences which mark the final stage in the subdivision of the arterial system, and the first stage in the convergence of the veins. The arterioles are the immediate feeders of the capillaries. Their special function is to regulate the flow of blood through the various capillary areas. They do this by decreasing in caliber (*vaso-constriction*) and thus increasing the resistance to the flow through the regions in which constriction occurs, or by increasing in caliber (*vaso-dilatation*) and so offering less resistance to the flow of blood. (The arterioles are supplemented in their regulatory action by the capillaries themselves and by the venules, as will be shown in later paragraphs.) The diversion of blood from one region to another is made necessary by changes in relative metabolic requirements. A fact fundamental to the physiology of the circulation is that there is not nearly enough blood in the body nor enough power in the heart to provide all the tissues simultaneously with enough blood for their maximal metabolic needs. Through the action of the arterioles blood is shunted more or less completely from inactive to active regions. In the table on page 273 the great capillary areas subject to increase or decrease in blood content are given as the *skeletal muscles*, the *skin* and the *abdominal viscera* (known as the *splanchnic area*, because innervated through the splanchnic nerves). For our present discussion the *brain* is added as a fourth region, because, while not subject to variations in *blood content*, it is subject to marked variations in *circulation volume* in response to variations in metabolic activity (page 351). The various *glands*, digestive and endocrine, form a fifth group which requires a certain amount of special discussion in connection with the provision of an adequate blood supply for the functional metabolism of gland action (page 137).

The Vaso-motor Mechanism.—The designation which forms the paragraph heading is used as a general term to cover the entire mechanism, muscular and nervous, by which the caliber of the

arterioles is controlled. The reflexes involved are spoken of as *vaso-motor reflexes.*

Vaso-constrictor and Vaso-dilator Neurons.—The special feature of the arterioles, as already brought out (page 287), is that their caliber is under strict neuromuscular control. The nerves belong to the autonomic system. We have already seen that the autonomic system consists of two subsystems with opposing actions (page 129). For the arterioles the *sympathetic* neurons are excitatory; they cause the circular muscle coat to contract, and hence the caliber of the arterioles to diminish. They are called *vaso-constrictor* neurons. The vessels of the skin, the splanchnic area, and most glands have rich vaso-constrictor innervation. Those of the skeletal muscles and brain have little or none.

The *parasympathetic* neurons are inhibitory. Under their influence the muscle fibers relax and the caliber of the vessels increases. These neurons are known as *vaso-dilators.* The vaso-dilator innervation of the bucco-facial region (salivary glands, skin of the face, buccal mucosa) and of the erectile tissues belong to the parasympathetic system proper. The dilator neurons to the abdominal organs are in part carried in the vagi, which are parasympathetic trunks, but also in part in the splanchnics, which are sympathetic trunks. The dilators to the skeletal muscles and skin elsewhere than on the face cannot be shown anatomically to belong to the autonomic system at all. They are closely related to the afferent (receptive) fibers. It appears in fact that many of the same neurons that carry impulses inward from the periphery to the central nervous system also carry vaso-dilator impulses outward from the central nervous system to the vessels of skeletal muscles and skin (page 338). This conduction of impulses outward in neurons that also carry impulses inward is known as "antidrome" conduction. It is interesting, not only as an economical means of achieving results, but also for its bearing on theories of nervous conduction.

The Vaso-constrictor Center.—A definitely localized area in the medulla near the fovea inferior of the fourth ventricle is identified as the *vaso-constrictor center.* Like the cardio-inhibitory center already described (page 303), it is in continuous tonic activity. The tonic state is thought to be maintained in part by the stimulating action of substances in the blood, but mainly reflexly, *i. e.*, through the constant play upon the center of nerve impulses passing through the medulla. The effect of the tonic activity of the center is to keep the arterioles that have constrictor innervation, *i. e.*, those of the splanchnic area, the skin and the glands, in a state of partial contraction, so that they offer considerable resistance to the flow of blood through them, but not so much as they are capable of, if the center is further excited.

Pressor Influences.—Influences that increase the activity of the center over and above its normal level are known as *pressor* influences. The test of a pressor influence is a rise in arterial pressure. Studies on experimental animals indicate that the pressor effect is brought to bear only over certain particular paths within the central nervous system. For example, the path up the spinal cord for pressor influences arising in somatic (non-visceral) receptors is confined to the apex of the posterior horn (substantia gelatinosa Rolandi) and the overlying tract of Lissauer (Ranson and associates). Pressor influences from visceral receptors pass up by a different path (Davis), probably either in the lateral or ventral funiculus. These pressor paths are not very sensitive. They can be aroused only by voluminous streams of nerve impulses, consisting of many separate impulses per unit of time. The receptors that appear regularly to generate sufficiently voluminous impulse streams are those of pain and cold. (The latter may act on the center indirectly, through the temperature-regulating center, page 447.)

Intellectual activity, particularly when of a type that arouses interest, and affective states associated with a threat to bodily well-being, *i. e.*, anger, fear and anxiety (page 735), are attended by a rise in arterial pressure. The conclusion is that the voluminous streams of nerve impulses involved in these mental conditions penetrate to the medulla and exert a pressor influence on the constrictor center.

Depressor Influences.—Any influence that operates to decrease the tonic activity of the constrictor center is known as a *depressor* influence. The criterion would logically be a fall in arterial pressure. But this criterion cannot be applied without caution, for active vaso-dilatation (page 337) has the same effect on arterial pressure as depression of the constrictor center. Before a true depressor influence can be postulated it must be shown that the fall in pressure has actually been due to a lessening of the activity of the constrictor center. The best-marked example of true depression is obtained by strong stimulation of the depressor nerve trunk (page 307). When a sufficiently voluminous impulse stream passes up this trunk there is true depression of the constrictor center with drop in arterial pressure. The nerve received its name on account of this property. The action is protective. As pointed out in Chapter XVIII, the afferent neurons which make up the depressor trunk arise in the heart and aorta and are stimulated powerfully when arterial pressure rises to excessive height. The depressor effect on the constrictor center acts in conjunction with the excitatory effect on the cardio-inhibitory center (page 307) to restore the normal level of arterial pressure when it has been raised unduly

from any cause whatever. These together constitute a major factor in the compensatory mechanism by which a fairly uniform arterial pressure is regularly maintained (page 330). There is evidence that in some animals the splanchnic nerve trunks may convey truly depressor influences, arising in visceral receptors. The warmth receptors in the skin (page 512) have also been looked upon as sources of true depressor influences. Positive evidence seems not to have been obtained.

Function of the Vaso-constrictor Center.—We look on the vaso-constrictor center as a factor in regulating the supply of blood to the various capillary areas in accordance with their relative metabolic requirements. Its action has two chief features. In the first place the more active it is the higher the general arterial pressure tends to rise; in the second place the more tendency there is for blood to be diverted out of the splanchnic area, the glands and the skin into other areas. Reference to page 273 shows that blood diverted out of these areas must be accommodated largely in the skeletal muscles. The other significant capillary area, the brain, has little possibility of change in *blood content*, because its enclosure in the cranial cavity permits neither of expansion nor contraction except within very narrow limits. Any change in general arterial pressure is necessarily reflected, however, in a corresponding change in the velocity of the circulation of blood through the brain, and hence in a change in *circulation volume* through the organ. The net result of an increase in activity of the vaso-constrictor center is thus a tendency toward improvement in the circulation through the skeletal muscles and brain at the expense of the splanchnic area, the skin and the glands. The extent to which the skeletal muscles actually accommodate increased quantities of blood depends on other factors, to be discussed presently. If no vascular dilatation occurs in them the effect of vaso-constriction in the splanchnic area, the skin and the glands is simply a rise in arterial pressure, the chief result of which is an equivalent increase in the circulation to the brain. In general, it may be aid that such pressor influences as tend to cause both mental and muscular activity are followed by increases in circulation both to brain and muscles. Such as tend only toward mental activity are followed only by a rise in general arterial pressure, with an equivalent increase in brain circulation.

The best-known depressor influences are purely protective to the heart, as already stated (page 307). It is probable that influences arising from the splanchnic area in connection with the digestive process are truly depressor as well. It is known, at least, that relaxation of the arterioles in the splanchnic area, with a corresponding drop in pressure, occurs commonly after meals, and is essential to good digestion. Mental states associated with bodily

comfort and relaxation may also possibly act to depress the constrictor center. Vaso-motor changes associated with the regulation of body temperature are discussed under that heading (page 446).

The Vaso-dilator Center.—Evidence has been presented for the existence of a definite vaso-dilator center in the area postrema, about 3 mm. behind the vaso-constrictor center (Ranson). This center is assumed not to be in continuous tonic activity. If the assumption is correct it means that the center is not responsive to the general stream of nerve impulses passing through the medulla. In experimental animals the center is found to respond to impulse streams composed of comparatively few separate impulses per unit of time (Martin and others). There is also evidence that the path of excito-dilator impulses up the cord is in the lateral funiculus (Ranson and Billingsley), separate from the pressor path to the vaso-constrictor center. Positive vaso-dilation, as distinct from depression of vaso-constriction, occurs in skeletal muscles and in glands as they become functionally active, in the erectile tissues during sexual excitement, or reflexly through sensory stimuli arising in the genitalia, and in the skin and mucous membranes under a series of conditions, including such affective states as embarrassment, skin stimulation due to warmth, and gentle mechanical skin and muscle stimulation, as in massage.

Functions of the Vaso-dilator Mechanism.—As a factor in adjusting the circulation to the metabolic requirements of the active muscles the vaso-dilator mechanism supplements the vaso-constrictor in preparing the muscle tissues to receive the augmented blood flow which vaso-constriction of the splanchnic and skin areas makes available. There is adequate evidence that positive dilatation occurs in the small vessels of the muscles whenever they become active. Positive vaso-dilatation occurs also in the glands. These structures are relatively small in man, and positive dilatation occurring in them insures them a copious blood supply without particular disturbance of the general circulation. Blushing is ordinarily assumed to be due to positive dilatation of the facial vessels brought on by autonomic discharges of emotional origin. Vaso-dilatation in the erectile tissues is a specialized reaction, dependent, as stated above, on definite conditions related to sexual activity. The efferent parasympathetic path to the erectile organ in dogs and some other mammals is in a separate trunk known as the nervus erigens. There is no evidence to indicate that the dilator neurons of this nerve are connected particularly with the vaso-dilato· center. The outflow of dilator impulses appears to be either a reflex in which only the lower part of the spinal cord is involved or to depend on complex p·ychical conditions involving many higher brain structures (page 750). The relation of vaso-dilatation to temperature regulation is discussed elsewhere (page 449).

Local Vaso-dilator Reactions.—Various irritants produce local vaso-dilatation, often preliminary to inflammation, when applied to sensitive areas of skin or mucous membrane. It has been shown that this action is not due to a direct effect of the irritant on the bloodvessels, nor is it a reflex in the true sense. The irritant acts on the terminations of sensory nerves in the skin. The resulting impulses reach the bloodvessels by axon branches which serve normally as the path of "antidrome" vaso-dilator conduction (page 334). The probable arrangement is indicated in Fig. 40.

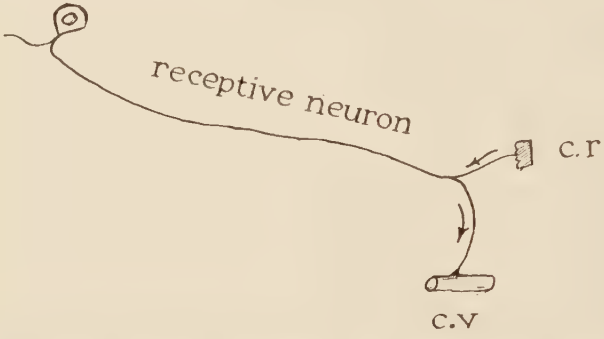

Fig. 40.—Diagram illustrating the nervous path by which skin irritation causes local vaso-dilatation. *c.r.*, cutaneous receptor; *c.v.*, cutaneous bloodvessel. Arrows indicate course of impulses. (After Bruce.)

Reactions of this type are known as axon reflexes. They are not, however, reflexes in the proper sense, since they involve no passage of synapses and no participation of any part of the central nervous system (page 120).

Summary.

Arterial pressure is the pressure exerted by stretched arteries on their contained blood. The chief factors determining its value are circulation volume and peripheral resistance.

The maximum pressure in the arteries occurs during ventricular systole. It is designated *systolic pressure.* The minimum pressure, known as *diastolic pressure,* occurs just before the reopening of the semilunar valves in the next systole. Mean arterial pressure usually lies somewhat below the half-way point between systolic and diastolic. The difference between systolic and diastolic pressures is called "pulse pressure."

The average value of systolic pressure in young adult males is about 125 mm. Hg. After middle life the average is 10 mm. higher. In women the pressures average 10 mm. Hg. lower. When pressures higher than normal are obtained the condition is designated clinically as *hypertension;* when lower than normal, as *hypotension.*

The wave of distention that travels down the arteries at each heart-beat is the *pulse*. The peak travels with a velocity of 6 to 7 meters a second. As the pulse advances, it becomes smaller, due to the absorption of the kinetic energy of the heart-beat by the stretching of the arterial walls. The decrease in size is accentuated by the increase in surface of arterial walls which results from the branching of the system.

The arterioles are the feeders of the capillaries. Their special function is to regulate the flow of blood through the various capillary areas.

Decrease in arteriole caliber is *vaso-constriction*. Increase in caliber is *vaso-dilatation*. The neuromuscular mechanism controlling arteriole caliber is the *vaso-motor* mechanism.

For interpreting vaso-motor phenomena the capillary system is divided into five areas – skeletal muscles, splanchnic area (abdominal viscera), skin, brain and glands.

Autonomic sympathetic fibers to the arterioles are *vaso-constrictor*. They are distributed mainly to the vessels of the skin, the splanchcic area and the glands. They arise from a *vaso-constrictor center* in the medulla which is in constant tonic activity. Influences which increase the activity of the center above its normal level are *pressor;* these that decrease its activity below its normal level are *depressor*.

Autonomic parasympathetic fibers to the arterioles are *vaso-dilator*. They are distributed to the bucco-facial region, the erectile tissues and portions of the abdominal region. The abdomen also receives dilator innervation in part by way of the splanchnics, which are sympathetic trunks. The dilators to the skeletal muscles, and to the skin elsewhere than in the face, are apparently receptive neurons which by "antidrome conduction" innervate the arterioles of those regions. A *vaso-dilator center* in the medulla is thought to exist, but not to be in tonic activity.

Pressor influences on the vaso-constrictor center tend to the diversion of blood from the splanchnic area, the glands and the skin, into the skeletal muscles. This action implies a receptive dilatation of the bloodvessels in the muscles. In the absence of such receptive dilatation, or in its presence if the center is sufficiently active, there is a rise in general arterial pressure which increases circulation volume through the brain. Depressor influences on the center are in large part protective to the heart. There are probably significant depressor effects in connection with the increased blood flow to the splanchnic area during digestion, and in mental states associated with bodily relaxation.

The function of the vaso-dilator center appears to be largely to promote the circulation of blood through skeletal muscles and glands by inducing positive arteriole dilatation in them. Vaso-dilation in the erectile tissues seems to depend on a mechanism that is

largely or wholly separate. There are significant vaso-motor changes, both constrictor and dilator, associated with temperature regulation.

Local vaso-dilatation of skin vessels may be produced by the action of irritants on receptive nerve endings in the region. The dilatation is brought about by so-called "axon reflexes." The course of the nerve impulses is over axon branches, by which "antidrome conduction" is normally mediated.

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CHAPTER XXI.

CIRCULATION: CAPILLARIES; VENULES; VEINS; SPECIAL FEATURES; LYMPH FLOW.

THE CAPILLARIES.

The blood flow through the capillaries is the significant blood flow of the body. Each individual capillary serves as the source of supply of materials and as the medium of reception of waste products and surplus heat for a quite definite group of adjacent cells (Fig. 26, page 246). If these are muscle cells, gland cells or nerve cells, their metabolism is subject to considerable or even great variation, as they pass from a resting to an active state or *vice versa*. In muscle cells, and perhaps to some extent in gland cells as well, the resting metabolism is pitched on so moderate a scale that a continuous flow of blood is not necessary for sustaining it. Corresponding with this fact is the observation (Krogh), that in muscle tissue while at rest fewer than one in ten of the capillaries are open at one time (page 289). Furthermore, the capillaries open out in rotation, so that each group of cells in turn has its environment renewed at intervals by interchange of materials with flowing blood. Between times the cells are depleting their environment of oxygen and food materials and charging it with waste metabolites. The temperature both of cells and environment is also rising. When in course of time adjacent capillaries open out there is a rapid interchange of material and an escape of surplus heat, thus preparing the cell groups for another period of no blood flow.

Capillaries Open Widely in Active Tissues.—In contrast with the small number of capillaries (200 or so per sq. mm.) open simultaneously in resting muscle, stands the large number (2000 per sq. mm. more or less) open in active muscle (page 289). Various agencies are known that may conceivably act to cause the opening. Among them should be noted positive vaso-dilatation through the nervous system. There is direct evidence that the capillaries respond to nervous stimulation in the same general manner as the arterioles; that positive dilation of arterioles accompanies muscular activity has already been pointed out (page 337). Another possible agency exists in the acid metabolites which tissues give off continuously, and in augmented amounts when active. It is interesting that this agency, which by analogy with the respiratory mechanism (page 374) would be expected to play a foremost part in adjusting the capillary circulation to metabolic needs, seems to be wholly indifferent, so far as studies of the effects of changes in

hydrogen-ion concentration in experimental animals have shown. About the only other agency that suggests itself is lack of oxygen. This will soon make itself felt in any cells cut off from interchange relationships with flowing blood, and very promptly if the tissues are active. Krogh and his associates have shown experimentally that oxygen lack does cause closed capillaries to open. How oxygen lack operates is not yet known. The fact that it shifts the metabolism toward an anaërobic basis suggests that special chemical substances may be given off to which the dilatation is due. In oxygen lack we have an agency which would appear adequate to account both for the opening out of the capillaries in active tissues, and also for their opening in rotation in structures at rest.

Effect of Histamine.—A noteworthy contribution to our understanding of capillary circulation was made through the discovery (Dale and Richards) that histamine (alone or as representative of a group of substances) causes all capillaries (and venules) exposed to its influence to open out widely. The profound changes in the circulation thus induced are discussed in a later paragraph (page 350)

Other Reactions of Capillaries.—Capillaries in regions subject to vaso-constrictor innervation appear to take part in the vaso-constrictor reactions that occur there. They also share in vaso-dilator reactions (page 337). Capillaries of particular areas of the skin can be caused to dilate actively by stimulation of sensory nerves to the regions (antidrome conduction). This possibility is strikingly exemplified in the disease *herpes zoster*, in which inflammatory changes in spinal ganglia give rise to localized capillary dilatations in the skin areas with which the ganglia have *sensory* connection. In the axon reflexes previously described (page 338), in which localized arteriole dilatation is produced by local stimulation, capillary dilatation takes place as well. Mechanical stimulation of the skin causes local constriction of the capillaries, usually followed after a few seconds by dilatation. Stimulation with ultra-violet radiation causes dilatation of the capillaries in the illuminated area. These last two effects are due to direct action on the capillary walls; no nervous structures are involved, so far as can be determined.

Capillary Pressure.—The blood in the capillaries is under sufficient pressure to maintain filtration (page 286). The existence of the pressure is due to the fact that the venules and even the large veins offer some resistance to the flow of blood through them, so that to keep the outflow from the capillaries at even pace with the input from the arteries a fair degree of pressure must be maintained in the capillaries. The pressure does not fluctuate with each heart-beat because by the time the pulse wave reaches the capillaries all the kinetic energy of the ventricular systole has been absorbed by the stretched arterial walls (page 332). The most satisfactory recent determinations of capillary pressure in man (sitting) give a range of 17.5 to 26.5 mm. Hg., with an average of 22 mm. The

pressure is somewhat lower when lying down and somewhat higher when standing. These determinations are of the pressure in capillaries of the skin. They are made by a device (Danzer and Hooker) in which the capillaries are brought into view under a microscope by applying oil to the skin. The skin is then compressed until the movement of blood in the capillaries ceases, and the compression released until movement just begins. The pressure at this instant is noted and considered to represent true capillary pressure. The figures given above are for *net* capillary pressures, *i. e.*, after allowance is made for the effect of gravity. If the vessel studied is below the heart the weight of a column of blood equal to the distance is deducted from the observed value; if above a corresponding addition is made. The maximum allowance does not exceed 10 mm. Hg. The effective filtration pressure is, of course, the actual pressure, not the net pressure as thus determined.

THE VENULES AND SMALL VEINS.

The venules differ from the capillaries structurally (page 289), particularly in features that affect permeability, so that we think of the point of merging of capillaries into venules as the point where interchange of materials ceases. (The possibility that some venules permit interchanges has been mentioned previously, page 290.) In regard to regulation of the blood flow through them by changes of caliber, the venules appear to act precisely like the capillaries with which they are continuous. There is evidence that nervous and chemical influences which cause constriction or dilatation of capillaries cause also constriction or dilatation of the accompanying venules.

The venules are distinguished from veins proper by having no smooth muscle in their walls. The small veins have a certain amount of muscular tissue. An interesting example of an effect due to this tissue is seen in the reddening of the skin when cold. Recent studies have indicated that skin color is more a matter of the venules than of the capillaries. When the skin is red the venules are full of blood; when pale they are nearly empty. When the skin is flushed with warmth there is dilatation of the venules along with the arterioles and capillaries, and blood flows rapidly through the skin. When the skin is red from cold there is sufficient constriction of the small veins (by direct action of the cold on the smooth muscle cells), so that in spite of positive vaso-constriction in arterioles, capillaries and venules blood is dammed back into the venules to some extent, a condition described as "passive congestion."

THE VEINS.

The obvious function of the large veins is to serve as channels for the return of blood from the capillaries to the heart. This function is not altogether simple, however. The flow of blood into

the heart is the main factor in determining the stroke volume, and indirectly the force of beat (page 319). The inflow depends on the pressure gradient between the blood in the large veins near the heart and the cavity of the ventricle at the moment of opening of the *A–V* valves (page 318). To maintain this gradient at a sufficient height to insure adequate filling of the heart the venous pressure must be kept up to about 10 mm. H_2O.

Since the veins are quite distensible and very slightly elastic, the maintenance of even this small pressure implies the presence in them of a good deal more blood than would just suffice to fill them. In other words, they are quite definitely overfilled, and must be kept overfull in order that the pressure shall not fall to so low a level that the heart in turn will fail to be filled. Most of the veins are supported more or less effectively by the tissues that surround them. If it were not for this outside support they would be distended a good deal more than they are in showing even the small pressure they do. Any given venous pressure signifies the presence in the large veins of a fairly definite amount of blood; the higher the pressure the more blood there must be in the veins. The same holds for the arterial system, as already pointed out (page 325). Since total blood volume is constant, any increase in blood content of either veins or arteries must be at the expense of other parts of the circulation. The significance of this fact is brought out in a later paragraph (page 349).

The Heart Can Sustain the Circulation.—If a person lies with the body exactly horizontal and without any motions, even of breathing, the circulation is maintained at a level sufficient to sustain life. This fact proves that the heart beats strongly enough to force blood all the way around the body, and back into itself again. The last action depends, as we have seen (page 318), on maintaining a certain pressure in the large veins, and the fact that a complete circuit is kept up under the conditions described, shows that the sheer power of the heart is sufficient for maintaining adequate venous pressure in addition to overcoming the arteriole-capillary-venule resistances in the path.

A continuous return of blood to the heart does not in itself prove that blood is flowing through all the open channels of the circulation. It is conceivable that the flow might restrict itself to certain short and easy paths, leaving the rest of the body unsupplied with fresh blood. So far as any individual organ or part of an organ is concerned, the question of whether blood will flow through it or not (assuming that there are open blood channels through it) depends on whether there is a pressure gradient, in other words, on whether the pressure in its artery is higher than in its vein. If there is a gradient blood will flow; the volume will be small if the gradient is low, greater if it is high, but there can be no complete stoppage in any region so long as there are some channels open and arterial

pressure is maintained. (It should be noted that on account of the abundant anastomosing of small arteries and small veins there are frequent stoppages or even reversals of flow through individual small anastomosing vessels, as the pressures at the two ends change with relation to each other. These can be seen readily in the frog's web. They are purely local phenomena, however, and do not affect the main situation as described above.)

Effect of Changes in Posture.—Since the heart beats with force enough to maintain the circulation when the body is horizontal, it should, in theory, do so equally well in any position (and would if the bloodvessels were not distensible). For each individual blood channel from the heart back to the heart again is in effect a U tube, in which the arms are of equal length. The arterial portion is one arm of the U, the arteriole-capillary-venule portion the base and the venous portion the other arm. It is a familiar fact of hydrodynamics that the weights of liquid in the two arms of a symmetrical U balance each other, so that the force of gravity exerts no influence on the movement of liquid through the system other than that due to the weight of the column to be moved. It follows from this that changes in posture should have no effect on the flow of blood through any of the vessels merely because they are now above and now below the level of the heart.

Gravity does enter as a factor, however, because of the distensibility of the vessels, chiefly the veins, large and small. Any vessel below the level of the heart distends under the combined action of two forces, one the pressure due to the heart's action and the other the weight of the column of blood between the given point and the heart. The distention continues until the stretch of the vessel plus the support of outside structures balances the combined distending forces. Obviously any circulatory U tube posterior to the heart will tend to become more distended, and so to contain more blood in it the more nearly erect the posture. In any individual blood circuit part of the heart's energy is consumed in imparting movement to the mass of blood, and part in overcoming the resistance offered by the circuit. The greater the mass to be moved, the more energy must be expended in that part of the action. Consequently more cardiac work must be done in moving the blood through the circuits in the legs when the body is erect than when it is recumbent, and through the arms when hanging down than when held up. This increase in the amount of blood to be moved against a peripheral resistance that has not changed would mean a slower blood flow if the arterial pressure were to remain also unchanged. As a matter of fact, the increased heart-rate seen in the erect posture usually raises the arterial pressure enough so that the rate of flow does not fall off excessively.

Compensation in the Splanchnic Area.—Many of the veins of the abdominal viscera have little outside support from surrounding

tissues. The chief bar to their indefinite distention is their own resistance. It is an important fact that the small veins of the splanchnic area are provided with a neuromuscular *venoconstrictor* mechanism, which acts to prevent them from becoming overdistended with blood while the body is erect. When one is lying quietly, and particularly when asleep, there is usually relaxation of tone in the splanchnic arterioles, due to lowering of the state of tonic activity in the vaso-constrictor center (page 334). There is also absence of resistance to distention in the small veins. The result is that the splanchnic area has in it more blood than usual, and capacity for still more if any force tending to cause it to take up more comes into action. When one changes to the erect posture from the recumbent gravity acts as a force to cause more blood to be accommodated in the splanchnic vessels. If the change in posture is made suddenly, as when one springs up out of sleep, considerably more blood than usual actually accumulates in the splanchnic area. The quantity is often great enough, in fact, to constitute a serious depletion of other parts of the circulation. There is likely not to be enough blood in the great veins to maintain adequate venous pressure. Then the heart will not be adequately filled, arterial pressure will fall, the brain will be inadequately nourished and dizziness or even faintness will result.

The tendency to this chain of untoward events is counteracted by increased constriction of the small abdominal vessels through a heightening of the tonic activity of the vaso-constrictor center. The stimulus to this increased tonicity is probably set up by the distention of the abdominal vessels. The compensatory reaction takes a long enough time to develop so that some symptoms indicative of an inadequate brain circulation are experienced by many persons every time they rise quickly from a recumbent to an erect position. In animals that go habitually on all fours the compensatory reaction is less marked. It is said that rabbits can be killed by holding them still in the vertical position, death being due to overlong anemia of the brain.

Accessories to Venous Circulation.—The compensation just described is barely adequate, or in some persons perhaps inadequate by itself to keep venous pressure as high as it must be to maintain proper filling of the heart when the body is erect. It is supplemented by two accessory mechanisms. The first of these is the combination of the valves in the veins with the massaging effect of bodily movements. All the veins except those of the trunk have valves along them at frequent intervals, usually at the point of union of two veins. These valves open toward the heart, so that if a vein is compressed with enough force to squeeze the blood from it the blood will be pushed toward the heart. Most bodily movements bring pressure to bear on one or more veins. Particularly do the muscles as they contract squeeze the blood out

of the small veins that permeate them. This "milking" of the blood toward the heart increases the pressure gradients from the arteries of the region toward the "milked" veins, and thus favors an improved blood flow. It is also a real factor in bringing enough blood into the large veins so that the heart shall be properly filled. Evidence of this is seen in the experience of persons who are compelled for one reason or another to stand very still for several minutes. The majority of persons in this situation presently become dizzy or even faint. The difficulty is promptly relieved by muscular activity, particularly of the legs and feet.

The second important accessory to the venous blood flow is the "bellows action" of the chest in breathing. The large veins of the chest are subjected to *intrathoracic* pressure, *i. e.*, the pressure of the lungs upon the chest contents. In all ordinary conditions this pressure is slightly below atmospheric (page 383). The explanation is given in Chapter XXIII. The movements of breathing set up rhythmic changes in intrathoracic pressure. In inspiration the pressure falls, in expiration it rises. The large veins are thus alternately more and less pressed upon in the chest. At each lessening of compression the flow of blood into them from outlying veins is favored. At each increase of compression the flow from the chest veins on into the heart is favored. There is thus a definite pumping action which undoubtedly is a significant factor in the flow of venous blood. The pumping action is accentuated in deep breathing, a fact that contributes markedly to the beneficial effects of breathing exercises.

In forced expiratory efforts with the glottis closed intrathoracic pressure may rise above atmospheric (page 384). The effect is obviously to obstruct the flow of venous blood through the chest. There is a damming back into the larger veins outside the chest. This is well illustrated by the engorgement of the large veins of the neck and face in a severe coughing spell.

DISTRIBUTION OF BLOOD FLOW.

The blood ejected from the heart passes around the circulation, distributing itself among the innumerable capillary paths in strict accordance with the relative resistances offered by them. The various mechanisms by which peripheral resistance is regulated, mechanisms that control arteriole caliber (page 333), capillary caliber (page 341) and venule caliber (page 343) are governed automatically in such fashion that the flow through the various tissues tends to be fairly closely adjusted to their individual metabolic requirements. In the resting body of a 70-kg. man the unit circulation averages about 7000 ml. (page 318). Some idea of how this flow is distributed among the various tissues is suggested in column 5 of the table below. The basis of the table is a series of observations by means of *stromuhrs* (Burton-Opitz and others) on the blood

flow per 100 gm. of tissue through various structures in lower mammals (dogs mostly). Unit circulation per kilo is about 50 per cent higher in dogs than in human beings (G. N. Stewart; also Bock and Buchholtz); the original observations on dogs have, therefore, been reduced by one-third in applying them to man. There is, of course, considerable liability to error in applying to man data obtained from lower mammals; but the relative metabolic requirements of various tissues (the brain perhaps excepted) are probably not widely different in men and mammals, hence the rough application attempted in this particular case is justified if not given more weight than intended.

The table brings out the fact that in the resting body the organs receiving a particularly copious blood flow per unit of mass are the kidneys, the brain and the liver (various small glandular organs, such as the thyroids and the salivary glands, have even higher blood flow per unit of mass, but their total mass is too small to justify their separate inclusion in the table). The skeletal muscles have a small unit flow when at rest, but, on account of their large total mass receive not far from a third of the entire blood flow. The portal organs have only a moderate unit flow, as these data show. No experimentally derived figures for the skin are available; the arbitrary assumption is made that skin circulation in the resting body is double that of the skeletal muscles per unit of mass.

TABLE SUGGESTING THE DISTRIBUTION OF BLOOD FLOW AMONG THE TISSUES OF A 70-KG MAN IN REST AND IN INTENSE EXERTION.

Tissue or organ.	Estimated mass in man, gm.	In rest.			In intense exertion.	
		Flow per 100 gm. per min. (dog), ml.	Estimated flow in man.		Suggested distribution in exertion, as due solely to vaso-motor adjustment, ml.	Suggested distribution including 5-fold increase in circulation, ml.
			Per 100 gm. per min., ml.	Entire tissue per min., ml.		
Skeletal muscle	31,500	12	8	2500	6000‡	30,000
Portal organs	2,600[a]	*30*	*20*	*520*	*100*	*500*
Liver	1,800	84	56	1000	200	1000
Kidneys	400	150	100	400	80	400
Skin	4,900	...	16*	800	200	1,000
Brain	1,400	136	100†	1400	420	2,100
All other tissues	...	...	...	900	100	500
				7000	7000	35,000

* Arbitrarily assumed to be double the blood flow of resting muscle.

† To allow for the presumably higher degree of brain activity in man than in the dog less than the *pro rata* reduction in blood flow is made for this organ.

‡ Tigerstedt cites observations showing active muscle to contain in the neighborhood of twice as much blood as resting muscle.

[a] Blood flow passes also through liver.

Blood Flow in Exercise. –The salient alterations in blood flow in exercise as compared with rest are: (1) A vasomotor redistribution favoring the active tissues; (2) a pronounced increase in circulation volume. To suggest the effect of vasomotor redistribution by itself column 6 of the table is presented. The experimental data available for use in this column are these: Tigerstedt cites evidence that active muscles may contain somewhere near twice as much blood as resting; the skin is known not to have less blood flow during exertion than during rest (as a matter of fact flushing of the skin accompanies muscular activity); finally, vaso-constriction has its main effectiveness in the splanchnic area. To allow for an approximate doubling of blood flow through the muscles, and at the same time assign to the skin and brain their indicated quota, the splanchnic tissues must be supposed to have their blood flow reduced to about one-fifth its resting value.

The effect of a five-fold increase in circulation volume is suggested in column 7 of the table. The particular points to be noted are: (1) The laboring muscles receive an augmented blood supply of the order of twelve-fold; (2) the brain circulation is materially improved; (3) the skin circulation (important in dissipating the large additional amount of heat liberated) is augmented also; (4) most of the other tissues receive about the same quantity of blood per minute as in the resting body. This latter point is significant as indicating that, while these tissues may not actually receive less blood than in the resting body, they do not get enough to permit them to function maximally at the same time that the skeletal muscles are so functioning.

There is more blood in heart, large arteries and large veins during activity than during rest. The amount ejected from the heart per beat may be more than doubled (page 318), implying an equivalent increase in blood content during diastasis. There must be more blood in the large arteries, since the greatly augmented unit volume can be moved around the circulation only by virtue of a heightened arterial pressure, and heightened arterial pressure involves more blood in the arteries than before (page 325). The increase in mean arterial pressure in vigorous exercise is apt to be about 50 mm. Hg. (from 105 to 110 mm. to 155 to 160 mm.). This is a little more than the average pulse pressure (page 329). The latter is due to the injection of about 100 ml. of blood into the arterial system. An increase in mean pressure of about the same magnitude implies about the same additional quantity of blood in the arterial system. We can conclude, therefore, that 100 ml. or so of blood are diverted from other vessels into the large arteries during vigorous exercise. The large veins must also contain more blood than before because otherwise the heightened venous pressure necessary to the maintenance of a greatly increased inflow into the heart could not exist.

The pulmonary area will contain more rather than less blood, because pressure in the pulmonary artery must be raised in order to drive the increased volume around the pulmonary circuit, and here again an increased pressure implies an increased content of blood; furthermore, Kuno has furnished direct evidence that the blood content of the lungs rises with increase in cardiac output.

The regions that show lessening of blood capacity through vaso-constriction are the abdominal and pelvic organs, the adipose tissues and the glands of the neck and head, *i. e.*, the thyroid and salivary glands. This lessening of capacity is the sole means by which blood is made available for filling up the dilated regions. No evidence seems to be at hand to indicate how completely these tissues can deplete themselves of blood by vaso-constriction. The estimates in the table recognize the fact that they cannot suspend function entirely during muscular exertion. The demands on the liver, as a matter of fact, are greater than usual, since increased consumption of sugar is going on.

Whether these particular estimates are strictly correct or not, the important fact comes out clearly that only a fraction of the potential blood capacity of the muscles can be occupied. When all the vessels of the skeletal muscles are fully dilated they probably have capacity for more blood than there is in the body; in other words, they can probably dilate to at least five times their resting volume. The estimates in column 6 of the table suggest that a doubling of their usual volume is probably nearly as great an increase as can be effective.

For purposes of illustration the estimates for the blood flow in exercise are designed to represent an extreme condition. When the exercise is more moderate the increase in circulation volume is less and the capillary widening and accompanying arteriole dilatation are confined to a smaller mass of muscle tissue. Under these circumstances the relative widening is probably much greater than when more muscles are active. In fact, it may be enough, added to such augmentation of the heart as occurs also, to give a blood flow amounting to thirteen times or more the resting value; in other words, enough to care for the maximal oxygen consumption observed experimentally, without involving any greater oxyhemoglobin dissociation than is seen in resting tissues (page 219). A fact of great importance about the nutrition of active muscles, however, not affected by the above statement, is that in sustained and vigorous activity even of a small muscle mass lactate production probably always outstrips the delivery of oxygen, giving rise to an "oxygen deficit" (page 91).

Blood Flow in Traumatic Shock.—In a former paragraph (page 342) the fact is noted that histamine produces extreme capillary and venule dilatation in all parts of the body, but notably in the abdom-

inal area. The obvious effect of a dose of histamine is the retention of an undue proportion of the blood of the body in the capillaries and venules. This may cut down the amount of blood available for filling the large veins below the point essential to adequate filling of the heart, and with the filling of the heart thus reduced there is partial failure of the circulation. Direct experimentation shows that the whole primary cause of the failure is inadequate inflow of venous blood into the heart, due, as already pointed out (page 343), to the fact that the large veins have not enough blood in them to keep venous pressure at the necessary level. Neither the heart nor the vaso-motor mechanism proper is impaired during the early stages.

During the World War it was conclusively shown that a state of collapse often seen in wounded soldiers, particularly after long exposure to cold and wet, is the result of circulatory failure of the type just described, and due to the action of histamine or a histamine-like substance produced in injured and lacerated tissues and set free into the blood. The designation *traumatic* shock indicates the fundamental relationship of trauma (tissue injury) to the state of collapse. The condition sets up a "vicious circle" in that the circulatory failure leaves the tissues unoxygenated, and the effect of their oxygen lack adds itself to that of the histamine-like substance to bring about more extreme dilatation. The most satisfactory immediate treatment yet suggested short of blood transfusion itself, consists of introducing a saline solution to bring up the blood volume, the solution being kept from escaping promptly from the vessels by the addition of gum acacia (page 271). So-called "surgical shock" and shock due to severe burns and scalds are essentially similar in origin and nature to wound shock, and come also under the designation "traumatic shock."

CIRCULATION THROUGH SPECIAL REGIONS.

Circulation Through the Brain.—The brain circulation offers several features of special interest, all centering about the necessity of maintaining a copious blood flow through an organ enclosed in an unyielding case. The immediate source of arterial blood is the "circle of Willis," formed by the union of the two internal carotids and the two vertebrals. From the circle of Willis arteries penetrate to all parts of the brain substance, subdividing ultimately into capillaries. The returning veins pass from the depths of the organ to its surface where they merge into the *venous sinuses*. These are spaces between folds of the dura mater, or in certain parts of the skull, between the dura mater and the cranial bones themselves. The main system of sinuses drains chiefly through the lateral sinuses into the internal jugular vein.

The cranial cavity is completely filled with its liquid or semi-liquid contents, which are as nearly incompressible as such substances always are. There is accordingly no way to introduce any additional liquid except by displacing some already present. The cerebrospinal fluid, which fills the ventricles of the brain, and the subarachnoid spaces of the brain and cord (page 359) may be displaced from the skull cavity into the spinal canal to the extent of a few milliliters. Only to this precise extent can the quantity of blood within the brain be increased. It may be taken as an established fact, then, that the outflow of blood virtually just balances the inflow instant by instant (the Monro-Kellie doctrine). Since vaso-dilatation and constriction are thus not factors in the regulation of the blood flow, it follows, as already stated (page 336), that the blood supply to the brain is directly proportional to the velocity of flow through the cranial vessels. The velocity, in turn, varies with the arterial pressure (strictly with the pressure gradient between arteries and veins).

Intracranial Pressure.—Since the cranial cavity is completely filled with incompressible fluid pressure on any one spot must be communicated undiminished to all other equal areas. From this it would seem that the high pressure in the arteries, tending to stretch their walls, would be transmitted across the brain substance to the veins, whose walls are under much lower stretching force, with the result of squeezing the veins more or less completely shut. As a matter of fact, there is some compression of the veins from the arteries in this manner, but the location of the veins, and particularly the arrangement of the venous sinuses, is such that they are not closed off enough to hinder the brain circulation by any arterial pressure short of the point of vessel rupture.

An increase in the quantity of material in the cranial cavity, such as may come from the growth of a tumor, hemorrhage from a ruptured vessel or the accumulation of cerebrospinal fluid (page 359), necessarily puts all the cranial contents under increased pressure. So long as this intracranial pressure is below arterial pressure the flow of blood is not seriously impeded. Whenever it rises above arterial pressure, however, the circulation is blocked, and brain anemia, with loss of consciousness, results.

The Pulmonary Circulation.—The pulmonary circuit is composed, like the systemic, of arteries, arterioles, capillaries, venules and veins. In general the same factors as affect the systemic circulation act also on the pulmonary, but on a smaller scale. The pulmonary arterial pressure is determined by the volume ejected from the right heart per unit of time, and by the peripheral resistance. The volume for any period of more than a few heart-beats is the same as is ejected by the left heart (page 318). The resistance is very much lower, however, so that the pressure is much less. There

are vaso-motor nerves to the pulmonary arterioles, by which their caliber may be changed, although it is doubtful whether any tonic action of the vaso-constrictor center is exerted on them. The capillaries and venules presumably react to such chemical agents as histamine very much as do the corresponding systemic vessels. The pulmonary vein is a much smaller reservoir for filling the left heart than the great veins of the trunk are for filling the right. It follows that if for any reason the right heart fails for as much as a single beat to keep the pulmonary circuit filled the left heart will be unable to eject its normal quantity, and a drop in systemic arterial pressure will occur.

The striking special characters of the pulmonary circulation are due to volume changes in the small vessels, which changes accompany, and in fact are the mechanical result of, the movements of the lungs in breathing. As the lungs are inflated in inspiration, their walls are stretched (page 383). This stretching brings traction to bear on the small vessels. The effect at first is to enlarge them, but as inflation continues this passes over into a diminution in volume, partly due to a change in shape of the expanding alveoli and partly to over-stretching lengthwise which cuts down the caliber disproportionately (Cloetta). During expiration these changes in volume of the small vessels are reversed; there is first an increase, followed toward the end of expiration by a decrease.

The effect on pulmonary blood flow is that during each respiratory cycle there is a period in which the capacity of the pulmonary circuit is steadily increasing. The left heart is, therefore, failing to get all the blood the right heart ejects, and systemic arterial pressure is falling slightly but steadily. This period coincides with the late part of expiration and the early part of inspiration. During the remainder of the cycle the capacity of the pulmonary circuit is decreasing; the excess blood is being squeezed out into the pulmonary vein, and so the left heart is getting more blood than the right heart ejects. During this period systemic arterial pressure rises. The resulting "respiratory waves" are conspicuous features of most arterial pressure tracings as obtained on experimental animals. It is an interesting index of the sensitiveness of the cardio-compensatory mechanism (page 306) that an increase in heart-rate accompanies every phase of falling pressure, and a decrease every rising phase.

Velocity of Pulmonary Blood Flow.—The time required for blood to pass around the pulmonary circuit in man is estimated in the same way as total circulation time (page 320), *i. e.*, by dividing the volume of blood in the pulmonary vessels by the stroke volume of the heart, thus determining the number of beats necessary to propel the contained volume the whole length of the circuit. In the table on page 273 pulmonary blood volume is estimated at

about 500 ml. Although this is a smaller estimate than various investigators have made, it is quite as large as is permissible, since it assigns to the pulmonary circuit one-seventh of all the blood in the body (page 270), a higher proportion than most experiments on animals have indicated. (See Wiggers on Pulmonary Circulation.) Approximately, five heart-beats are required to move this quantity of blood. At average pulse rates this indicates a circulation time for the pulmonary circuit of slightly less than five seconds. Recent direct experiments have given 6.5 seconds as the average figure (Blumgart and Weiss). The gaseous interchanges between blood and alveolar air take place only in the capillaries, and the efficiency of the blood as an agency of transport depends in part on how thoroughly it comes into equilibrium with alveolar air (page 218). If the flow is too rapid there will not be time for complete equilibrium to be reached. Direct measurements of the velocity of capillary blood flow in frogs' lungs have been made by means of a microkinematograph (Krogh and Rehberg), with the result that a mean velocity of 0.12 mm. per second was observed. If this same velocity were to apply to human pulmonary capillaries the time spent in traversing them would be approximately four seconds (a mean length of 0.5 mm. is assumed). But this is so near the total estimated pulmonary circulation time as not to be possible if the latter is approximately correct. It appears necessary, therefore, to suppose the velocity to be considerably higher in the capillaries of the human lung than in those of the frog's lung. If the same velocity is assumed as estimated earlier (page 322) for human systemic capillaries, *i. e.*, 0.3 mm. per second, the time spent in traversing the pulmonary capillaries becomes about 1.6 seconds, which appears to be a reasonable proportion of the whole pulmonary circulation time.

Circulation Through the Portal Area.—The characteristic feature of the portal circulation is the presence of two sets of capillaries in tandem, one in the so-called "portal organs," the stomach, intestines (except the distal portion of the large intestine), spleen and pancreas; the other in the liver. In the resting body the vessels of the portal organs proper and also of the liver are fairly well dilated, hence the total resistance of the double capillary channel is not disproportionately great, and the portal blood flow is correspondingly copious.

The liver has a direct arterial blood supply through the hepatic artery, in addition to its venous supply through the portal vein. It is estimated that about two-thirds of the total blood flow of the liver is of portal origin and one-third of arterial origin. The first subdivisions of the hepatic artery merge with those of the portal vein in such fashion that the liver capillaries receive blood from both sources and carry a mixed stream of arterial and venous blood. An

interesting, and not satisfactorily explained, fact is that while the mean pressure in the hepatic artery is much higher than in the portal vein (90 to 100 mm. Hg. as contrasted with about 10 mm. Hg.) no tendency for the arterial pressure to extend itself backward along the portal channels in such a way as to obstruct the portal flow can be detected.

Evidence from experimental animals indicates that the vasoconstrictor innervation to the portal system exerts its main effects on the small vessels of the portal organs proper and only comparatively feebly on the vessels of the liver. Splanchnic stimulation, therefore, cuts down the flow of portal blood through the liver much more than of arterial blood. It is apparently on account of this fact that diversion of blood from the splanchnic area to the muscles can occur, as in exercise (page 349), without depriving the liver itself of sufficient blood flow to enable mobilization of sugar to go on.

Circulation Through the Kidneys.—Each kidney tubule has two important capillary areas, the capsule, with its contained glomerulus, and the secretory portion of the convoluted tubule. According to the picture of kidney function presented earlier (page 144), the glomerulus acts as a simple filter separating out from the blood plasma all substances in solution in it except proteins, phosphatides and allied compounds. The lowest glomerular pressure at which filtration will occur is that equal to the effective osmotic pressure of the non-filterable constituents of plasma, chiefly proteins and phosphatides (page 252). This pressure is about 30 mm. Hg. Above this minimum the effectiveness of the filter varies directly with the glomerular pressure. Each glomerulus is in essence a group of non-anastomosing capillaries springing from a single afferent vessel and converging into a single efferent vessel. The afferent vessel is larger than arterioles usually are, and springs more directly from a main branch of the renal artery. The efferent vessel is *smaller* than the afferent, a situation in sharp contrast with that seen in all other arteriole-capillary-venule sequences in the body, in which the venules are definitely larger than the corresponding arterioles. The net effects of the peculiar glomerular structure are two: (1) A decidedly higher capillary pressure than obtains elsewhere in the body, thus giving a particularly favorable mechanism for filtration; (2) a situation in which either vascular constriction or dilatation may either increase or diminish filtration according to where it is localized. Thus constriction of the *afferent* vessel obstructs the inflow of blood into the glomerulus more or less, and cuts down the pressure within it, so reducing the rapidity of filtration. Constriction of the *efferent vessel*, on the other hand, obstructs the outflow, raises the glomerular pressure and so increases filtration. Dilatation of the afferent vessel, by admitting blood

more freely to the glomerulus, tends to raise glomerular pressure and so favor filtration; dilatation of the efferent vessel favors the freer escape of blood, and thus tends to lower the pressure and cut down filtration.

It appears to be a general fact that the efferent vessel is more sensitive to constrictor influences than the afferent vessel (Richards). It follows that filtration is favored (a condition tending to diuresis; page 440) by *weak* constrictor influences, whether nervous or chemical. Strong constrictor influences, on the other hand, act on the afferent vessels as well as on the efferent, lessen the amount of filtration and so tend to reduce the quantity of urine. A similar relative sensitiveness of afferent and efferent vessels to dilator influences would tend to produce precisely opposite results. We encounter here an interesting fact, however, in that most substances that act chemically as dilators tend to escape so rapidly in the glomerular filtrate that not enough remains in the blood passing through the efferent vessels to dilate the latter, even though they may be more sensitive to the action than the afferent vessels. Thus chemical dilators are nearly all of them diuretics.

In addition to the vascular changes just described by which filtration through individual glomeruli is speeded up or cut down, it has been shown (Richards and associates) that in the normal kidney the number of functioning glomeruli may vary widely from time to time. Direct observations on frogs' kidneys have shown fields in which not more than one in five of the glomeruli have blood flowing through them. The injection of dilator substances into the blood stream is followed promptly by opening up of many or all of the previously inactive glomeruli. Constrictor substances like adrenin or postpituitary hormone have been seen, on the other hand, to cause active glomeruli to become inactive. There is evidence, furthermore, that individual glomeruli may become active or inactive more or less intermittently, and under the influence, apparently, of purely local conditions. There appears to be a rotation in function similar to that already described for the capillaries of skeletal muscle (page 341). It is obvious that in the arrangement for varying the number of glomeruli in action we have a means of providing for wider variation in total quantity of urine than would otherwise be possible, and more significantly, of providing for variations in quantity of urine without accompanying variations in composition (page 440).

Persons who have the misfortune to lose the function of one kidney may continue to eliminate normally for a lifetime. This is easy to understand in view of the large reserve of inactive glomeruli ordinarily present when both kidneys are functioning. After the removal of one kidney the other becomes permanently enlarged. This is probably wholly a vascular change, the increased proportion

of functioning glomeruli leading to an increase in the blood supply to the organ.

Richards and associates have shown also that some capillaries within individual glomeruli may close, lessening but not stopping the flow of blood through the glomerular tufts. The effect of this is to cut down glomerular filtration (page 144), hence to alter the composition of the urine under some conditions as well as to decrease its volume. Details are given on page 433.

LYMPH FLOW.

The more or less continuous passage of liquid by filtration from the blood plasma into the tissue spaces (page 286) implies an equivalent onward movement of tissue fluid. The tissue spaces are drained by a definite set of vessels, the "lymphatics," resembling veins in general plan and in being provided with valves, but on a much more delicate scale. It has been generally held that the tissue spaces open directly into the finest lymph channels, but modern histological investigation seems to have demonstrated that all the lymph vessels down to the very minutest are closed off from the tissue spaces by definite membranes. This finding has great theoretical significance, for it means that in the formation of true lymph all agencies that influence the passage of substances through membranes are brought into action. The practical bearing is mainly in connection with the factors having to do with the spread of disease-producing organisms through the body in the lymphatic system. So far as the normal functioning of the healthy body is concerned the chief significance is in the definite distinction thus established between tissue fluid and lymph proper. The actual draining of the tissue spaces depends primarily on the maintenance of gradients either of osmotic or hydrostatic pressure between the tissue spaces and the minute beginnings of the lymph channels; secondarily, on the maintenance of hydrostatic pressure between these channels of origin and the openings of the lymph vessels in the great veins near the heart. The hydrostatic pressure in the tissue spaces is virtually that in the capillaries, *i. e.*, around 22 mm. Hg. (page 342); the pressure in the great veins is usually less than 1 mm. Hg. (page 344). The condition thus exists for a movement of lymph toward the heart. As a matter of fact, in most parts of the body outside the splanchnic area the flow is exceedingly sluggish in the absence of bodily movements. When bodily movements occur, and particularly when the muscles are active, precisely the same massaging action comes into play as described formerly for the veins (page 346). The valves of the lymphatics promotes flow toward the heart just as do the valves of the veins. The aspiration of the thorax (page 383) is also a marked aid to the flow of lymph.

The lymphatics of the lower limbs and trunk unite in the "receptaculum chyli." From this lymph reservoir the thoracic duct extends up the trunk to an outlet in the vena cava, near the heart. The thoracic duct carries also the lymph flow from the left arm. The right arm and head have separate drainage in a main lymphatic of their own. The flow of lymph from the tissue spaces of the splanchnic organs is more abundant than from most other parts of the body. There is accordingly some movement of lymph in the thoracic duct at all times. During digestive activity the flow is markedly augmented.

Lymphagogues.—The quantity of lymph moving through the thoracic duct per unit of time will obviously be augmented by any agency that increases the quantity of fluid in the tissue spaces, and particularly in these spaces in the abdominal organs, whence the main thoracic duct flow is derived. Substances that have this effect are known as *lymphagogues.* In general they fall in two classes. Certain colloidal organic substances, present in crustacea and mussels, in strawberries and some other fruits, as well as elsewhere, make up the "first class" of lymphagogues, according to the terminology of Heidenhain. These substances act in susceptible persons to increase the permeability of the capillaries, particularly in the abdominal regions and skin. The escape of liquid from the blood to the tissue spaces, especially in the areas mentioned, is thus promoted. The flow through the thoracic duct augments in proportion to the increase in abdominal tissue fluid.

Lymphagogues of the "second class" are crystalloids, like ordinary glucose, which when injected into the blood in high concentration raise its osmotic pressure materially. The effect is to cause water to enter the blood from the tissue spaces (page 271). The blood volume is thus increased (a condition of true "plethora") and, as a necessary result, the hydrostatic pressure mounts in all bloodvessels. The capillaries of the splanchnic organs show a markedly increased filtration as the result of the heightened pressure within them. Thus the flow through the thoracic duct is augmented. Obviously this action does not relieve the plethora, for the thoracic duct flow returns at once to the blood. Actual relief depends on the restoration of the former osmotic pressure of the blood by the elimination of the substance which raised it.

Local Edema.—An accumulation of either tissue fluid or lymph in any part of the body, tending to cause more or less turgor and swelling, is known as *edema.* It may be either local or general. If the former it implies that the escape of liquid from the capillaries of a particular region into the tissue spaces is exceeding or has exceeded the capacity of the lymph vessels to drain the region. The common swellings due to sprains and bruises are due to augmentation of flow into the tissue spaces as the result of mechanical

injury to the capillary walls. The regions that show swelling are usually those that have poor lymph drainage. Local *skin* edema, as in urticaria (hives), implies an increase in permeability in some of the skin capillaries, frequently due to some lymphagogue of Heidenhain's first class.

General edemas involve pathological disturbances in bodily function, and their discussion is outside the scope of this book.

CEREBROSPINAL FLUID.

The ventricles of the brain, the central canal of the spinal cord and the subarachnoid spaces of the entire central nervous system are occupied by a characteristic fluid known as *cerebrospinal fluid*. The total quantity in man is estimated at 100 to 150 ml. The fluid has been described as essentially blood plasma minus its proteins. As a matter of fact this description is not strictly accurate, for there are traces both of proteins and phosphatides, and the concentrations of inorganic salts, of sugar and urea and of the innumerable other dissolved substances present in plasma may differ slightly or in some conditions materially, in the two fluids. Very few cells (4 to 6 per c.mm.) are present in cerebrospinal fluid. It is clear and only slightly viscous, and does not clot.

In the normal body the cerebrospinal fluid is produced mainly by exudation (in the opinion of most investigators the exudative process is a true act of secretion) from the choroid plexuses in the ventricles of the brain. From the fourth ventricle the fluid issues into the subarachnoid spaces by way of the foramina of Magendie and Luschka. There are probably small contributions to the fluid from perivascular spaces in the subarachnoid regions.

Definite evidence exists that the formation of cerebrospinal fluid by the choroid plexuses is continuous. (The production of internal hydrocephalus as a result of blocking of the aqueduct of Sylvius is an important item.) Since the total amount present remains practically uniform, this implies an equally continuous removal. Experiment has shown the path of removal to be chiefly by way of the arachnoid villi directly into the venous sinuses (Weed); there is also a small amount of passage into the lymphatic channels.

The cerebrospinal fluid is under a pressure of about 8 to 9 mm. Hg. This is considerably below the pressure of blood in the vessels of the choroid plexuses. If the formation of the fluid is purely a filtration process the difference must be great enough to counteract the osmotic pressure of the blood proteins, *i. e.*, 30 mm. Hg. or more. (See Glomerular Filtration, page 355, for analogy.) To the extent to which active secretion enters as a factor in forming the fluid the pressure gradient may be less. The relatively low pressure of the cerebrospinal fluid is still probably at least 5 or

6 mm. Hg. above that of the blood in the venous sinuses. The osmotic pressure of the fluid is also lower than that of the blood by an amount equal to the osmotic pressure of the blood proteins, a fact favorable to passage of the fluid into the venous blood. The conditions essential to a continuous formation of the fluid in the choroid plexuses and its continuous return to the venous sinuses are thus seen to be fulfilled. The normal rate of formation is not known. When the subarachnoid space is opened, as in basal fracture of the skull, or by lumbar puncture, as much as 200 ml. a day may escape to the outside. The conditions are then so different from normal, however, that no trustworthy estimate of the usual rate of formation can be based on the observation.

The cerebrospinal fluid surrounds and encloses the central nervous tissues, but does not appear to permeate them. It is not the tissue fluid of the nervous system, therefore. It is conceivable, and in fact probable, that the surface cells carry on interchanges of material with the adjacent fluid, but the prime function of the fluid cannot be considered nutritive. In fact the most plausible function suggested for it is that it serves as a cushion and shock absorber for the delicate nervous tissues. Pathological conditions involving the meninges lead to marked alterations in the character of the cerebrospinal fluid. These are of diagnostic value.

Summary.

The blood flow through individual capillaries is adjusted more or less completely to the metabolic requirements of adjacent tissues. In resting muscle this adjustment, so far as the capillaries themselves are concerned, consists of a rotation of capillary function. Fewer than one-tenth of the capillaries opening out at one time. The mechanism of the rotation is not altogether clear. There is evidence that lack of oxygen is potent in causing closed capillaries to open. In active tissues most of the capillaries are open. Capillaries react to various influences. The extreme dilation induced by histamine is a striking instance.

Capillary pressure (cutaneous) averages around 22 mm. Hg. in man, sitting.

Venules differ from capillaries mainly in that their walls are impermeable. Their reactions to nervous and chemical influences are on the whole similar to those of the capillaries with which they are continuous. *Small veins* have some smooth muscle in their walls by which their caliber may be changed.

To insure adequate filling of the heart the pressure of blood in the veins must be kept up to about 10 mm. H_2O. The maintenance even of this slight pressure in the large veins requires that they be distended with blood. They cannot endure even moderate depletion without serious ill effect on the circulation.

The heart is able to sustain the circulation in the body in the horizontal position without any adventitious aids. In the erect posture the veins below the level of the heart distend with blood under the influence of gravity, increasing the burden on the heart in moving the blood through the circuits of which they are part. The possible distention in the splanchnic area due to gravity is sufficient to threaten the maintenance of the circulation. Overdistention is prevented normally by a compensatory veno-constriction. Accessories to venous circulation are the massaging effects of bodily movements and muscular contractions, and the aspiration of the thorax in breathing.

The distribution of blood among the tissues in the resting body is, on the whole, such as to enable the various tissues to carry on their resting metabolism. In muscular exercise there is a redistribution in favor of the laboring muscles. The increase in total circulation is sufficient, however, to make up for much or all of the loss due to diversion of blood to the muscles, so that probably none of the tissues receive much less during muscular exertion than during rest. The central nervous system and skin receive a good deal more.

In *traumatic shock* extreme capillary and venule dilatation occur. The effect is to reduce so materially the quantity of blood available for filling the large veins that the heart is inadequately filled and circulatory impairment or even failure results.

The volume of *circulation through the brain* depends almost wholly on the velocity of blood flow in the cranial vessels. This in turn depends on the general arterial pressure. Local vaso-motor changes within the brain have little or no significance. Increase in intracranial pressure does not impair brain circulation seriously until it becomes as great as arterial pressure. At or above this level the brain circulation is blocked.

The *pulmonary circulation* is subject to the same main influences as determined the character of the general circulation, but on a smaller scale. Pulmonary arterial pressure is much less than aortic pressure. With every change in the degree of lung inflation in breathing the capacity of the small pulmonary vessels changes. The result is a respiratory fluctuation in the flow of blood from the pulmonary system into the left heart, causing a coincident fluctuation in systemic arterial pressure.

The *portal circulation* includes the capillary areas of the portal organs proper and of the liver in tandem. In the resting body the resistance offered by this double capillary channel is moderate and the blood flow is, therefore, copious.

The *liver* receives about two-thirds its blood supply through the portal vein and the remaining one-third through the hepatic artery. The blood from the two sources becomes mixed in the liver capil-

laries. Vaso-constriction in the splanchnic area affects the portal organs proper more than the liver. It follows that the flow of blood from the hepatic artery is less reduced than that from the portal vein, and even in marked splanchnic vaso-constriction the liver receives a considerable blood flow.

The *kidney glomeruli* have a structure that favors exceptionally high capillary pressure. The rate of filtration through the glomeruli varies directly with the capillary pressure in them. By differential action of constrictor and dilator agencies on the afferent and efferent vessels respectively the capillary pressure is subject to delicate adjustment. Weak constrictor influences tend to increase filtration, and so bring on diuresis, by acting predominantly on the efferent vessels. Strong constrictor influences, on the other hand, by acting on the afferent vessels, tend to cut down the urine flow. Dilator substances generally filter rapidly through the glomerular membranes. Their only seat of action is, therefore, the afferent vessels, and they accordingly function as diuretics.

The number of functioning glomeruli is ordinarily only a fraction of the total number present. Dilator substances cause many more to open out. Constrictor substances cause many that were previously open to close. The quantity and concentration of urine depend in part on the number of glomeruli in function.

The *lymphatic system* appears to be a closed system, separated from the tissue spaces in which it has its fine beginnings by delicate membranes. The result is that true lymph is distinct from tissue fluid. The movement of lymph through the lymphatic vessels depends primarily on the existence of a higher hydrostatic pressure in the tissue spaces than at the outlets of the lymphatic system in the great veins. Massaging action, due to bodily movements and to muscular contractions, and the aspiration of the thorax promote the flow materially.

Lymphgogues increase lymph flow either by making capillaries more permeable (Heidenhain's first class) or by inducing a state of plethora and so raising capillary pressure (Heidenhain's second class).

Local edema implies a formation of tissue fluid or of lymph in excess of the ability of the lymphatics of the region to drain it off. Mechanical or chemical injuries to capillaries in regions of poor lymph drainage cause the majority of local edemas.

The *cerebrospinal fluid* is formed continuously by exudation (or true secretion) from the choroid plexuses in the ventricles of the brain. It circulates through the brain ventricles and the subarachnoid spaces and passes back into the venous blood mainly by the arachnoid villi into the sinuses; to a small extent, into lymphatic channels.

Cerebrospinal fluid contains only traces of proteins and phos-

phatides. In other respects it is similar to blood plasma, although not agreeing in detail. It functions apparently as a cushion for the central nervous system rather than as a nutritive fluid for its cells.

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CHAPTER XXII.

THE RESPIRATORY MECHANISM; THE ACT OF BREATHING; THE MAINTENANCE OF A NORMAL ALVEOLAR ATMOSPHERE.

Respiratory Essentials.—In previous chapters the three essentials to proper supplying of oxygen to the tissues and removal of carbon dioxide from them have been emphasized as *normal blood* (page 262), a *sufficient circulation* (page 283) and *adequate lung ventilation* (page 218). The first and second of these have been dealt with in earlier chapters. The present chapter deals with the third.

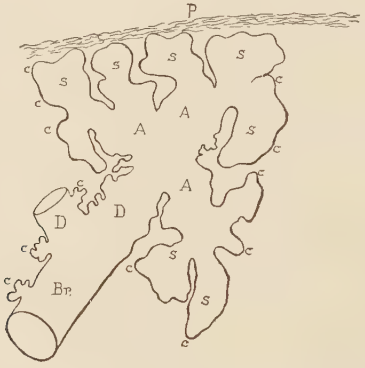

FIG. 41.—Diagram of lung lobule. *Br.*, terminal bronchiole; *S*, *S*, alveolar air sacs; *c*,*c*, alveoli proper. (After Miller.) (From Howell: A Text-book of Physiology, W. B. Saunders Company, Publishers.)

The Alveoli and Normal Alveolar Atmosphere.—Adequate lung ventilation implies the maintenance in the lung alveoli at all times of an atmosphere in which the oxygen pressure is approximately 100 mm. Hg., and the CO_2 pressure approximately 40 mm. Hg. (page 218). Acting against the maintenance of such an atmosphere are the continuous movement of oxygen out of the alveolar air into the blood and entry of CO_2 from the blood into the alveolar air.

The alveoli are minute recesses along the margins and at the tips of only slightly less minute air ducts. These, in turn, are subdivisions of larger bronchioles, which unite into still larger, and so on out to the main bronchi, that arise by bifurcation of the trachea.

FACTORS IN LUNG VENTILATION.

There is open communication, although by a narrow and more or less tortuous passage, between each alveolus and the outer atmosphere (assuming the glottis and nasal passages to be open). It follows that simple diffusion of oxygen inward and of carbon dioxide outward must contribute somewhat toward maintaining the alveolar atmosphere, without any aid from breathing movements.

As a matter of fact simple gaseous diffusion comes much nearer sufficing for the purpose in the resting body than one would be apt to think possible in view of the narrowness of the smaller air passages. The proof of this statement is that if a gentle current of atmospheric air is caused to flow over the bifurcation of the bronchi, so that the concentrations of oxygen and CO_2 at that point are continuously those of atmospheric air, no further lung ventilation is necessary in the resting body, simple diffusion from the bifurcation sufficing to maintain an adequate alveolar atmosphere, at least in enough alveoli to sustain life. It follows that if the respiratory tree were shorter by about the length of the air passages (the alveoli remaining uncollapsed) breathing would be unnecessary, so long as one kept perfectly quiet. This method of artificial respiration (known as "intratracheal insufflation") has considerable application in surgery of the chest and in other situations in which chest movements are to be dispensed with.

Since diffusion is not quite adequate for maintaining a suitable alveolar atmosphere in the resting body, and grossly inadequate in activity, it must be supplemented by *positive lung ventilation*. The supplementing agency is the *act of breathing*.

Action of the Diaphragm in Breathing. -Breathing is in essence a rhythmic change in chest capacity brought about by muscular activity. The chest is bounded posteriorly by the diaphragm; anteriorly and at the sides by the rib cage and associated structures. The diaphragm is a sheet of muscle with a central tendon and fibers radiating outwardly. It is pressed upon from below by the liver and stomach, which are pressed upon in turn by the other abdominal organs and by the firm muscular abdominal wall. The net result of the abdominal pressure, so far as the diaphragm is concerned, is that it takes somewhat the contour of a nearly flat inverted basin. Active contraction of the diaphragm flattens it further, forcing the liver and stomach downward, and displacing somewhat the other organs of the abdomen. These displaced organs make room for themselves in turn by stretching the abdominal walls. When the diaphragm relaxes the elastic return of the abdominal walls forces the organs back to their former position. By active contraction of the abdominal muscles the liver and

stomach can be forced considerably further into the chest space than usual, pushing the diaphragm ahead of them, and incidentally stretching it beyond its usual degree of tension. Contraction of the diaphragm enlarges the chest in its antero-posterior diameter. Active contraction of the abdominal muscles decreases the chest in the same diameter below its resting size.

Action of the Respiratory Muscles of the Chest. -The normal position of the ribs with reference to their attachment to the vertebral column is at a downward slant, so that if the rib cage as a whole is lifted, bringing the ribs nearer to a right angle with the axis of the body, the dorsi-ventral diameter of the chest increases. Furthermore, the axis of attachment of each rib to its vertebra is at an angle of about 45 degrees with the sagittal plane. The effect of this angle is that as the rib cage is lifted the individual ribs rotate outward, increasing the lateral diameter of the chest. This action is particularly effective in the mid-chest.

A number of muscles of the chest are so attached that their contraction tends to lift the rib cage, and so to increase the capacity of the chest in the two diameters indicated above. These muscles as a group make up the *inspiratory* muscles of the chest. Chief among them are the *external intercostals* and the *serratus posticus superior*. Some of the muscles at the forward end of the thorax, notably the *scalenes,* are thought to aid the action by fixing the first and second ribs so that the pull of the intercostals shall not be nullified in whole or in part by a yielding of these forward ribs.

The costal cartilages, the ligaments about the attachments of the ribs, the muscles of the chest and the structures within, all show some degree of elastic resistance to distortion. The position of the chest when no breathing movements are going on is necessarily, therefore, the position of least elastic strain. This is the position to which it will return whenever any agencies that have forced it into a different position cease acting. A purely passive expiration is thus bound to follow every act of inspiration. This passive process may be supplemented by active contraction of a group of *expiratory* muscles. These include chiefly the *internal intercostals* and the *serratus posticus inferior*. By the contraction of these muscles the chest may be forced to a smaller size than it takes passively. In labored breathing these expiratory muscles of the chest and the abdominal muscles as well act to carry expiration beyond its passive level. It is thought by some investigators that the expiratory muscles always come into action to some extent even in ordinary quiet breathing. They play an important part in the regulation of the outflow of air from the lungs in *voice production*. It appears that quiet breathing is normally carried on mainly by the diaphragm (abdominal breathing), but if tight clothing is worn chest movements (costal breathing) may do most of the work.

Lung Capacity.—The lungs occupy all the space in the chest cavity not taken up by other structures. This space varies widely in different individuals, according to the size and configuration of the body. The average lung capacity, *i. e.*, the volume of the air spaces, with the chest in the resting position, is given as about 2600 cc. By an extreme expiratory effort the capacity can be reduced by about 1600 cc. to a residue of 1000 cc. This latter volume of air, which remains in the lungs when the chest has been collapsed as fully as possible by muscular effort, is known as *residual air*. The difference between this and the air in the chest when in the resting position, about 1600 cc., is known as *supplemental air*. An ordinary quiet inspiration increases the capacity of the lungs by about 500 cc. on the average. This quantity of air, which flows into and out of the lungs with each quiet breath, is known as *tidal air*. An extreme effort of inspiration increases chest capacity considerably more. This figure is more variable than the figure for tidal air. It averages about 1600 cc. The air taken in by this extra effort is known as *complemental air*. The sum of complemental air, tidal and supplemental air, in other words, the total amount that can be exhaled after an extreme effort of inspiration, is the *vital capacity*. The value of this item is looked upon by some observers (Dreyer) as an index of physical fitness.

Alveolar Air and the "Dead Space." -Not all the air in the lungs is in the alveoli, *i. e.*, in direct exchange relationships with the blood. The large and small air passages hold part. These passages make up the so-called "dead space." This dead space must be taken into account in studying lung ventilation for two reasons. In the first place the air that enters the alveoli at the beginning of an inspiration is not fresh atmospheric air, but air that was left in the air passages at the end of the previous expiration. Only after this air that has already been in the alveoli once is swept back into them again does any fresh atmospheric air begin to enter. In the second place the lung does not expand uniformly throughout at each inspiration, but opens out region by region. The action has been described as resembling somewhat the manner of opening of a lady's fan (Keith). The effect is that in quiet breathing, in which only about one-fourth of the potential expansion is actually being brought into play, part of the small air passages open out well, admitting air freely to their contributary alveoli; the rest change little or none, and the alveoli into which they lead get only the indirect benefit that comes from the renewal of the air in the large passages. Some use is made of the air in the dead space by diffusion of oxygen and carbon dioxide in and out of the alveoli, but at the best the lung ventilation is considerably less effective than it would be if there were no dead space.

Casts of the bronchial tree made on the cadaver indicate an

average for the dead space of about 140 cc., or more than one-fourth of the tidal air. This figure is of uncertain value as indicative of the dead space in the living lung, for the smaller air passages all have smooth muscle in their walls by which the caliber of the passages can be changed, and these muscles are under the control of the autonomic nervous system. Vagus stimulation causes contraction and sympathetic stimulation relaxation of the bronchial musculature. The symptoms of bronchial asthma are due to the narrowing of the small air passages by spasms of this musculature. Conditions leading to a general out-pouring of sympathetic nervous discharges (anger, fright, etc., page 735) bring about a general widening of the air passages. The dead space is increased thereby, but the breathing is also always much augmented, so that the greater ease of flow of air into and out of the alveoli presumably more than counteracts the lessening of efficiency due to the increased dead space.

The gross value of the lung ventilation per unit of time is obviously the product of the number of breaths drawn by the average quantity of air taken in at each breath. (To obtain the net value due allowance must be made for the effect of the dead space.) In adults during waking and when the body is at rest the respiratory rate is about 12 a minute, and the volume of each breath (normally the tidal air, page 367) amounts to somewhere around 500 cc. The total lung ventilation per minute is then about 6000 cc. The oxygen content of this quantity of air is about 1260 cc. Assuming one-fourth of this oxygen to be unavailable because it does not get beyond the dead space, we have about 950 cc. of oxygen actually entering the alveoli per minute. The blood takes up about 300 cc. in the same time (page 215), leaving 650 cc. to be exhaled in the expired air. This remainder does not represent an overventilation, because the significant factor in the uptake of oxygen by the blood is the *oxygen pressure* in the alveoli, which, as already pointed out (page 217), has to be maintained at about 100 mm. Hg. in order to insure approximate saturation of the hemoglobin.

Gas Pressures in Alveolar Air.—The total gas pressure in the alveoli is necessarily equal to atmospheric pressure (760 mm. Hg.) when the glottis is open and the chest stationary. This pressure is made up in part of gases breathed in, and in part of water vapor and carbon dioxide given off from the blood. The water vapor, with which the alveolar air is saturated, has a partial pressure of about 47 mm. Hg. (at 760 mm. Hg. barometric pressure); the CO_2 has a partial pressure of about 40 mm. Hg. Deducting these from 760 we have 673 mm. Hg. as the partial pressure exerted by the air entering the alveoli from outside. If the air entering the alveoli kept all its oxygen, which it does not, the partial pressure of the oxygen in it would be given by $\frac{X}{160} = \frac{673}{760}$ (1), in which X is the

calculated partial pressure of oxygen at 673 mm., 160 being the pressure of the same gas at 760 mm. Solving this equation gives X = 142. But the air as it enters the alveoli promptly loses oxygen at such a rate as to leave only about 650 cc. for every 950 cc. taken in. The oxygen pressure, therefore, falls in the same proportion and the actual oxygen pressure is obtained from the equation: $\frac{X}{142} = \frac{650}{950}$ (2). Solving this equation, we obtain for the partial pressure of oxygen 97 mm. Hg. This is the approximate minimum oxygen pressure in the alveoli under the particular conditions stated above, *i. e.*, water vapor tension of 47 mm. Hg., CO_2 pressure of 40 mm. Hg., a volume of breathing that delivers 950 cc. of oxygen to the alveoli per minute, and a flow of venous blood through the lungs of a percentage hemoglobin saturation (page 218) and at a rate such that 300 cc. of oxygen are taken up each minute.

The only approximately obligate constant in the above list of conditions is the partial pressure of water vapor, which is uniform because always at saturation. The CO_2 output from the blood and the oxygen uptake by the blood depend on the diffusion gradients between alveolar air and blood. These in turn depend on the relation between CO_2 and O_2 tension in the venous blood as it enters the pulmonary capillaries, and the CO_2 and O_2 pressures in the alveolar air. The tensions of these gases in the blood are affected by changes in bodily metabolism (page 219). The pressures of the same gases in alveolar air are determined by the lung ventilation. The flow of blood through the lungs depends on the circulation volume, and is therefore subject to the influences which determine circulation volume (page 318).

Long Ventilation is Adjusted to Metabolism. One of the exceedingly significant phenomena of physiology is the close adjustment maintained among these variable factors, some circulatory and others respiratory, whereby every shift in bodily metabolism operates to bring about precisely the circulatory and respiratory changes needed for carrying on the metabolism efficiently at the new level. The mechanism of control of the circulatory changes has already been outlined (Chapter XVIII). The respiratory control consists of regulations of the lung ventilation in such fashion that however the CO_2 and O_2 content of the venous blood entering the pulmonary capillaries may change, the oxygen and carbon dioxide pressures in the alveolar air are kept near 100 mm. and 40 mm. Hg. respectively. The mechanism of this control is discussed in Chapter XXIII.

Alveolar-air Determinations.—The equations given above for calculating the gas pressures of alveolar air assume the functional dead space to be known. As a matter of fact, however, no method of arriving at the functional dead space directly has yet been devised, hence the composition of alveolar air cannot be computed

on the simple basis of measurements of the quantity of air breathed and determinations of the loss of oxygen from and uptake of carbon dioxide by the same. It is necessary, instead, to determine the composition of alveolar air by direct experimentation, and by calculation backward to obtain an estimate for the value of the functional dead space. The desired determinations on alveolar air present no particular difficulty except that of getting a truly representative sample. The method of Haldane and Priestley for obtaining such a sample consists of exhaling forcibly, at the end of a period of strictly normal breathing, through a tube about 4 feet long and 1 inch in diameter. A side outlet in this tube near the end into which the subject blows leads directly into a collecting pipette. The side outlet is opened and the air sample taken after at least 800 cc. of air have been expired. This method gives consistent and reliable results, provided the breathing prior to the forced expiration has been normal. The great stumbling block to all quantitative work on the respiratory exchange is the sensitiveness of the breath-control mechanism to volitional and affective influences (page 373). This sensitiveness makes it hard to be certain that the breathing under experimental conditions is always the same that it would be in precisely the same metabolic state, with the subject not under observation.

Types of Breathing.—Although the only accurate method of indicating the character of the lung ventilation is by stating the volume of air respired per unit of time, a general idea can be gained from a description of the breathing. For the purposes of this description certain technical terms have been adopted. Normal quiet breathing, in which the tidal air only is being respired, and the rate (in adults) is not more than about 12 to 15 per minute, is *eupnea*. For any given individual the lung ventilation in eupnea is quite constant. Changes in posture influence the value somewhat. The range for different individuals is wide. Figures as low as 5.1 and as high as 13.2 liters per minute are cited by Y. Henderson and Haggard from a group of normal adults. The average, as indicated earlier, is about 6 liters.

A temporary suspension of breathing, such as may be induced by various means as described below (page 380), is *apnea*. An increase in lung ventilation, either by a quickening of the rate or an increase in the depth of inspiration, or both together, is *hyperpnea*. The distinction between eupnea and hyperpnea is clear, in that the former is definitely the unconscious breathing of the resting body, and represents the undisturbed lung ventilation of basal metabolism, while the latter represents either the lung ventilation of a higher level of metabolism, *i. e.*, of functional metabolism superposed on basal, or the interposition of special nervous or chemical influences whereby the breathing is augmented. A marked increase

in the depth of individual respirations, so that the breathing becomes definitely labored, is *dyspnea*. The essential feature of dyspnea is marked involvement of the expiratory muscles, so that forced expirations are added to deep inspirations in imparting depth to the respirations as a whole. No sharp line can be drawn between hyperpnea and dyspnea. In fact, the two terms are primarily descriptive of different things. It is true that hyperpnea does not mount very high without the concurrence of dyspnea. This is seen clearly in the labored breathing of severe exertion; it follows from the fact that the drawing of deep breaths is a main factor in securing maximal lung ventilation. It is possible, however, for dyspnea to occur with little or no hyperpnea, as when labored breaths are drawn at long intervals; a condition seen in late stages of asphyxia and in some diseases.

Summary.

Adequate lung ventilation implies the maintenance in the alveoli of an atmosphere in which the oxygen pressure is about 100 mm. Hg., and the CO_2 pressure about 40 mm. Hg.

Simple gaseous diffusion contributes somewhat toward lung ventilation. It is supplemented by the positive ventilation maintained through the act of breathing.

Contraction of the diaphragm enlarges the chest in the antero-posterior diameter. The contraction displaces the abdominal contents downward and outward, putting the abdominal walls under distention. The elastic recoil of these walls restores the diaphragm to its former position. Positive contraction of the abdominal muscles forces the diaphragm further into the chest than usual. This action is seen in forced expiration.

Elevation of the rib cage by contraction of the *inspiratory* group of muscles enlarges the chest in its dorsi-ventral and lateral diameters. The ensuing elastic strain on various chest structures serves to return the chest to its resting position; quiet expirations are therefore largely if not wholly passive. A group of *expiratory* muscles can force the chest to a still smaller size. These function in forced expirations. They act also to regulate the outward movement of air in voice production, and are thought by some investigators to play a part in expirations usually considered passive.

The capacity of the lungs in the position of rest averages about 2600 cc. This is subdivided into 1000 cc. *residual air* (that remaining after extreme expiration), and 1600 cc. *supplemental air* (that expirable by forced expiration at the end of normal expiration). About 500 cc. enter and leave the lungs in quiet breathing. This is *tidal air*. A further extreme effort of inspiration brings in about 1600 cc. more, which is *complemental air*. The sum of complemental air, tidal air and supplemental air is *vital capacity*.

The air passages make up the *dead space*, so-called because the air in these passages has no direct relationship with the blood in the pulmonary capillaries. The dead space reduces considerably the efficiency of lung ventilation. Its volume is stated to average about 140 cc. in the cadaver. In life the volume is variable on account of the smooth muscle in the walls of the bronchioles. Out-pouring of parasympathetic impulses causes bronchio-constriction; of sympathetic impulses, bronchio-dilatation.

The gross lung ventilation for any period is the product of the number of breaths by the average volume per breath. On account of the dead space the net ventilation is only about 75 per cent of the gross. Calculation shows that the ventilation in ordinary quiet breathing is adequate to supply the amount of oxygen required for metabolism, and at the same time to maintain alveolar oxygen pressure at a value which insures virtual saturation of the hemoglobin of the blood.

Variations in metabolism are accompanied by parallel variations in lung ventilation, so that however the O_2 and CO_2 content of the venous blood entering the pulmonary capillaries may change the oxygen and carbon dioxide pressures in the alveolar air are kept near 100 mm. and 40 mm. Hg. respectively.

In the absence of precise knowledge as to the volume of the functional dead space it is necessary to know the composition of alveolar air in order to make accurate calculations of the respiratory exchange. The method of Haldane and Priestley for getting a reliable sample of alveolar air is described.

Normal quiet breathing is designated *eupnea*. A temporary suspension of breathing is *apnea*. An increase in lung ventilation is *hyperpnea*. A marked increase in the depth of individual respirations, with pronounced involvement of the expiratory muscles, is *dyspnea*.

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CHAPTER XXIII.

THE RESPIRATORY MECHANISM: THE CONTROL OF BREATHING.

THE MECHANISM OF BREATHING.

The muscles of breathing are skeletal muscles that differ from other skeletal muscles in the body in no known respect save that possibly the phase of recovery (page 87) is more rapid in them than in others, and so the susceptibility to fatigue less. They do not contract unless stimulated. Their normal source of stimulation is the central nervous system and the channels of stimulation are ordinary motor nerves (page 104). Every breathing movement implies an antecedent discharge of nervous impulses. The muscular contractions are tetanic in character, determined as to force by the number of fibers brought into play (page 86), and continuing as long as the impulse streams persist. Like other neuromuscular mechanisms composed of somatic motor nerves and skeletal muscles, the muscles of breathing can be excited both reflexly and volitionally. A familiar example of a breathing movement of reflex origin is the gasp one gives on stepping under a cold shower. The ability to excite breathing movements volitionally is too obvious to require comment.

Automatic Excitation of the Respiratory Mechanism.—Unlike other neuromuscular mechanisms made up of somatic nerves and skeletal muscles, the respiratory mechanism is subject to spontaneous rhythmic excitation. In other words, a stream of nervous discharges, neither volitional nor reflex in origin, is set up at regular intervals over some or all of the neurons composing the nervous part of the mechanism. If for any reason the stream fails to be set up we have the condition of apnea (page 370); streams of such intensity as to evoke only the inspiration of tidal air, and timed at a rhythm of about 15 per minute, give eupnea; more frequent streams or streams involving more neurons give hyperpnea; the inclusion of copious discharges to expiratory muscles, so timed that the normal movement of expiration is deepened, constitutes dyspnea.

In analyzing these impulse streams in respect to their origin and in respect to the factors that determine their frequency and volume we are analyzing the mechanism by which lung ventilation is adjusted to the metabolic requirements of the body.

THE RESPIRATORY CENTER.

An area in the medulla at the level of the calamus scriptorius is identified as the locus of the *respiratory center, i. e.,* as the immediate source of origin of the respiratory discharges. No particular group of cells in the area has been described as making up the center, but there is abundant evidence showing that so long as this particular area is intact respiratory discharges continue regularly, while injury to it is followed by prompt cessation of these discharges. The center is bilateral. That is to say, the respiratory muscles of the right side are excited from the right half of the medulla and of the left side from the left half. Notwithstanding this fact, and the further fact that each half is presumably composed of a great many nerve cells, it is necessary to treat of the center for purposes of discussion as a functional unit.

Acid Control of the Respiratory Center.—The first problem to present itself is that of the actual cause of the nervous discharges to which the center gives rise. A vast amount of study has been devoted to this problem. All workers are agreed that the excitation is chemical, and that it relates itself in some intimate way with the tensions of oxygen and of carbon dioxide in and around the cells of which the center is composed. Of the various detailed suggestions that have been presented, the one that appears to explain most satisfactorily the phenomena of breathing is that formulated by Gesell. According to this view, the cells of the respiratory center tend to discharge nerve impulses whenever the hydrogen-ion concentration within them rises above a certain critical level, and to discharge more and more actively the higher above this level the acidity rises. The critical level is probably not the same in all individuals, nor at all times in the same individual. It probably averages not far from a pH value of 7.35, perhaps ranging between 7.25 and 7.45 or thereabouts.

Factors Governing the Acidity of the Respiratory Center.—The immediate source of acid is in the metabolism of the cells themselves. In the presence of oxygen CO_2 will be formed continuously. If oxygen is lacking lactic acid will be formed instead. In either case the hydrogen-ion concentration of the cells tends to rise. Opposing the increase in acidity is the escape of CO_2 or other acid by diffusion from the cells to the immediately surrounding tissue fluids and thence to the blood.

The intensity of nervous discharge from the center, or whether it will discharge at all or not, depends thus on the balance between the production of acid within the center and its outward diffusion from it. We may assume the production of free hydrogen ions to be at a fairly constant rate (perhaps more rapid when oxygen is deficient than when it is abundant, page 378). The rate of outward diffusion

of acid depends on the tension of CO_2 in the blood (page 232). This tension, in turn, depends on another balance, namely, that between the production of acid by all the tissues of the body and the escape of acid by diffusion of CO_2 from the blood into the alveolar air. This diffusion of CO_2 is contingent on the lung ventilation. So long as the CO_2 pressure of alveolar air does not rise above about 40 mm. Hg. the CO_2 tension of arterial blood will not rise much above the same figure. It will then be possible for acid to escape from the respiratory center fast enough so that its hydrogen-ion concentration shall not much exceed a pH value of 7.35 or thereabouts. We thus see that the intensity of discharge of the respiratory center is conditioned by the CO_2 pressure of the alveolar air, other factors remaining constant.

Nervous Factors in Lung Ventilation.—According to the conception developed in the last paragraph, a degree of lung ventilation that keeps the CO_2 pressure of alveolar air at 40 mm. Hg. keeps or tends to keep the hydrogen-ion concentration of the respiratory center at about pH 7.35. Assuming the center to be of average sensitiveness, this means that it is continuously in a state tending to mild discharge. It is obvious that continuous mild discharge would have the effect of keeping such inspiratory muscle fibers as receive stimulation in a state of continuous tetanic contraction. Action of this sort would not accomplish lung ventilation. The latter depends on alternating increase and decrease in chest capacity. Some additional agency must function, therefore, to suspend the discharges of the center at regular intervals, allowing the chest to return passively to its resting position.

Investigation has shown that this agency is nervous, and that it consists of afferent impulses originating in receptors in the walls of the lungs, and passing to the medulla over axons in the vagus trunks. The receptors are stimulated as the lung walls stretch during inspiration. The impulses thus set up are inhibitory to the respiratory center. Thus as the inspiratory muscles contract as the result of discharges from the center, the lungs are distended and impulse streams antagonistic to these discharges are set up (the Hering-Breuer phenomenon). As soon as the antagonistic streams attain sufficient volume the discharges from the center are suppressed and the inspiratory muscles relax. The chest then collapses, the inhibitory impulse stream ceases or becomes negligibly small, and the center at once discharges again, starting another respiratory cycle.

MECHANISM OF HYPERPNEA.

This interesting mechanism is adequate, as described, to account for eupnea. It will account also for the *deeper inspirations* of hyperpnea, when of chemical rather than nervous origin. These

deeper inspirations are due to a more intense discharge from the respiratory center. They result, presumably, directly from increased hydrogen-ion concentration in the center, and indirectly, in most cases, from an increase in bodily metabolism. On account of the more intense influence back of the discharges a greater volume of antagonistic impulses must be generated in order to suppress them; hence the deeper inspiration before the breath comes to an end. To account for the *quickening of breathing* in hyperpnea an additional nervous mechanism is postulated. This is supposed to consist of a second set of afferent nerves from the lungs, stimulated when the lungs deflate. The impulses carried by these nerves are thought of as excitatory to the respiratory center, and hence as hastening its discharge. Actual evidence for the existence of nerve impulses aroused by lung deflation has been obtained only from lungs in extreme collapse. It seems necessary, in order to base an explanation of quickened breathing on the action of such nerve impulses, to assume that they are in fact aroused when the lungs deflate from any level beyond that ordinarily attained in eupnea. They are supposed to reinforce the regular discharges from the center in such a manner as to get the inspirations under way more quickly than otherwise. The path of these impulses is also by the vagus nerves. Sectioning these nerves in experimental animals results at once in a slower rhythm in which individual respirations are much deeper than before. The assumption ordinarily made is that this represents the result of rhythmic activity of the center under acid stimulation alone, and without any influence, either excitatory or inhibitory, from the lungs. The assumption implies a rhythmic change in hydrogen-ion concentration within the center at each breath marked enough to shift it from a condition of discharge to a condition of no discharge and *vice versa*. The occurrence of such a rhythmic change in acidity has yet to be demonstrated.

MECHANISM OF DYSPNEA.

The forced expirations of dyspnea are interpreted to mean that when the hydrogen-ion concentration of the respiratory center passes a second critical level, higher than that for inspiratory discharges, a second series of discharges is induced. These pass to the muscles of expiration, and hence over entirely different nerve paths from the inspiratory discharges. They are also timed differently, so as to fall in the expiratory phase of the breathing movements.

LUNG VENTILATION IN EXERCISE.

In violent exertion the tissues may pour CO_2 into the blood at the rate of 3000 to 4000 ml. per minute (page 233). The resultant interference with the escape of CO_2 from the respiratory center

promptly raises its acidity to a level of very intense discharge. The inspirations, therefore, become deep. When they are finally cut off by the inhibitory action of the inspiratory reflex the chest collapses, and in its collapse is carried forcibly beyond the point of passive return by the synchronous action of the expiratory muscles (some degree of dyspnea is assumed). The marked collapse arouses a pronounced expiratory reflex which, in turn, excites the center promptly to a new inspiratory discharge.

This combination of chemical and nervous influences acts with great efficacy to maintain lung ventilation at a level such that the CO_2 tension of alveolar air does not mount above 40 mm. Hg., even in violent exertion. The actual volume of air breathed in the latter situation may be 70 or 80 liters a minute (Henderson and Haggard report one record of 84 liters). At ordinary barometric pressure, *i. e.*, with the oxygen of the atmosphere at about 160 mm. Hg., this lung ventilation suffices fully to maintain an adequate oxygen pressure in the alveoli. That this is so can be shown by applying the equations on page 369 to the conditions present in exercise. The dead space and alveolar pressures of water vapor and CO_2 may be taken to be the same as during rest. The figure for the partial pressure of oxygen in alveolar air before deducting for oxygen consumption is therefore the same as given in equation (1). To derive the additional data needed for solving equation (2) we may assume an oxygen consumption of 4 liters a minute (page 221), and a lung ventilation of 70 liters a minute (see above). In 70 liters of air at 760 mm. barometric pressure there are about 14,700 ml. oxygen; after deducting 25 per cent for the effect of the dead space this leaves about 11,000 ml. A consumption by the body of 4000 ml. leaves 7000 ml. in the expired air. Equation (2) then becomes $\frac{X}{142} = \frac{7000}{11{,}000}$, and the value of X is 91 mm. Hg., a figure only slightly below the minimum alveolar oxygen pressure essential to oxygen saturation of the blood (page 217).

LUNG VENTILATION IN ANOXEMIA.

In a previous paragraph (page 374) emphasis is laid on the importance of the balance between acid production in, and acid diffusion from, the respiratory center as the determining factor in the discharges of the latter. A salient feature of Gesell's theory of respiration is that it explains the hyperpnea which develops in anoxemia as due largely to an interference with the escape of acid from the center, instead of attributing it altogether to some direct or indirect effect supposed to be exerted on the center by lack of oxygen, as other theories have generally done. The way in which anoxemia affects escape of acid, according to this view, is by decreas-

ing the amount of oxyhemoglobin in arterial blood (page 222). When there is less oxyhemoglobin than normal in the blood there will tend to be correspondingly less reduction to hemoglobin during the passage of the blood through the tissue capillaries. But much of the acid-carrying capacity of the blood depends on the decrease in acidity that attends the reduction of HbO_2 to Hb (page 164), acting in alternation with an increase in acidity as Hb is reconverted to HbO_2 in the lung capillaries. Any lessening of this alternating reduction and reformation therefore cuts down the ability of the blood to convey acid, and so tends to cause acid to accumulate in the respiratory center.

An additional factor in raising the acidity of the center in anoxemia is the partial substitution of anaërobic for aërobic metabolism, with some production of lactic acid (page 51). The conception of lactic acid removal in skeletal muscle (page 87) is assumed to apply to the respiratory center as well. According to this conception, about four-fifths of the lactic acid formed is normally got rid of by reconversion to carbohydrate, a process that does not give rise to excess CO_2. When oxygen is wanting the lactic acid is assumed not to be all reconverted. There is, therefore, an accumulation of acid out of proportion to the difference in amount of actual oxidation. This factor, in connection with the interference with escape of acid described in the last paragraph, accounts fully for the hyperpnea of anoxemia.

LUNG VENTILATION IN HEMORRHAGE AND IN OXYGEN EXCESS.

In hemorrhage there is a decrease in the ability of the circulation both to deliver oxygen to the tissues and to carry carbon dioxide away from them. The respiratory center is, therefore, affected in the same way as in anoxemia, and the hyperpnea of hemorrhage is explained similarly. A curious, and at first view apparently paradoxical, phenomenon is a hyperpnea that attends the breathing of pure oxygen at about 3 atmospheres pressure. The suggested explanation is that at this degree of pressure enough oxygen is in simple solution in the blood plasma to supply the metabolic needs of the tissues, and there is, therefore, no significant reduction of oxyhemoglobin. The acid-carrying power of the blood is lowered to an equivalent extent, and so the respiratory center suffers an increase in acidity to a degree sufficient to bring on hyperpnea.

ASPHYXIA.

The distinction between anoxemia and asphyxia is that in the former condition lack of oxygen is the salient defect, interference with the carrying away of carbon dioxide not being assumed to

occur. In true asphyxia, on the other hand, carbon-dioxide elimination is impaired as well as oxygen delivery. We have just seen that some interference with CO_2 escape is unavoidable in anoxemia, because of the lessening of oxyhemoglobin reduction, but this is small in proportion to the interference in true asphyxia, such as is seen in suffocation, as by choking, drowning or inhalation of smoke. The combined effect of oxygen lack and carbon-dioxide retention is obviously to raise the acidity of the respiratory center to an excessive level. Severe dyspnea ensues, becoming more and more violent, and culminating in convulsions. The respiratory center then shows signs of exhaustion; respirations become infrequent and long-drawn, and finally cease.

Artificial Respiration. After asphyxiation has gone to the point of cessation of respiratory effort it is necessary to ventilate the lungs by some artificial means in order to restore the respiratory center to a condition of activity. Various fairly effective mechanical devices for the purpose are in use in hospitals and relief stations. In the absence of any such the lungs can be ventilated by rhythmic compression applied directly to the chest. Needless to say in cases of drowning the water must be drained from the lungs before the artificial respiration is applied. Of the various procedures that of Schaefer is generally recommended. He describes it as follows: "It consists in laying the subject in the prone posture, preferably on the ground, with a thick, folded garment underneath the chest and epigastrium. The operator puts himself athwart or at the side of the subject, facing his head and places his hands on each side over the lower part of the back (lowest rib). He then slowly throws the weight of his body forward to bear upon his own arms, and thus presses upon the thorax of the subject, and forces air out of the lungs. This being effected, he gradually relaxes the pressure by bringing his own body up again to a more erect position, but without moving the hands." The movements should be continued at the rate of about twelve a minute for one-half hour or more if spontaneous breathing is not resumed sooner.

EFFECTS OF OVERVENTILATION.

It is easy to overventilate the lungs volitionally, by breathing more rapidly or more deeply than one would unconsciously. Various affective states, particularly anger and fright, are also attended typically by overbreathing. The effect is to make alveolar air approach the composition of atmospheric air more nearly than normal. (It is practically impossible to bring alveolar air to complete coincidence with atmospheric; the water vapor tension of the former will be considerably higher and its CO_2 pressure somewhat higher than the latter, and its oxygen pressure will be somewhat lower,

even in extreme overbreathing.) The increase in oxygen pressure is of little significance because the hemoglobin is nearly saturated at the lower alveolar pressure of ordinary breathing (page 217). The marked lowering of CO_2 pressure is of great significance. The normal alveolar CO_2 pressure of 40 mm. Hg. is only about 5 mm. below the CO_2 tension of venous blood. The diffusion gradient is moderate and the escape of CO_2 correspondingly gradual. Vigorous overventilation may reduce the CO_2 pressure of alveolar air to not over 5 mm. Hg. At the steep gradient thus set up CO_2 escapes much more rapidly from the blood than normal, and hence more rapidly than it enters the blood from the tissues. The effects, so far as the blood and tissues are concerned, have already been described (page 232). The lowered CO_2 tension of the blood favors the escape of acid from the respiratory center. The latter accordingly becomes insufficiently acid to discharge impulses, and diminished breathing or even apnea sets in. The duration of the apnea depends on the degree of overventilation of the lungs. In young children after a fit of temper it is often surprisingly long. In volitional holding of the breath acid accumulates in the respiratory center, and sooner or later the impulse to discharge becomes so intense that volition can no longer suppress it. When this point is reached breathing is resumed, willy nilly.

The Respiratory Quotient in Normal Breathing and in Overventilation.—The *respiratory quotient*, by definition, is the ratio by volume of the carbon dioxide given off in metabolism to the oxygen consumed. It is valuable as an index to the nature of the material being oxidized (page 458). In any type of breathing not involving pulmonary overventilation the carbon dioxide given off in expired air is very nearly equivalent, moment by moment, to that produced in the tissues, and the oxygen taken up from inspired air with that used by the tissues. It is thus possible to determine both the respiratory quotient itself and the nature and extent of the metabolism of the body as a whole by estimations of the above quantities. Such estimations form the basis of "basal metabolism" determinations (page 456). In practice fifteen-minute periods are generally deemed adequate except in very refined work. Several compact and efficient devices are in use for making the estimations.

Overventilation of the lungs does not effect the uptake of oxygen from inspired air, which continues to agree closely with that used by the tissues, but does affect the escape of carbon dioxide from the blood, so that the amount given off in expired air exceeds that produced by the tissues during the same period. Following a period of overventilation is a second period during which the blood is regaining its former CO_2 content; while this lasts the elimination of CO_2 in expired air is less than its production by the tissues. Estimations of the respiratory quotient during either of these

periods will obviously give results not truly representative of the metabolic state of the body.

Tabulation of Respiratory Data.—For the convenience of the reader a series of figures indicating the relative magnitudes of the various quantities and pressures (or tensions) of the gases concerned in the respiratory exchange are presented in the accompanying table. The data for eupnea are recorded averages; the other figures represent conditions readily realizable in a 70-kg. man.

TABULATION OF RESPIRATORY DATA.

	Vol. per breath, ml.	Breaths per min.	Vol. per min., ml.	O_2 uptake per min.	CO_2 output per min.	Respiratory quotient.
DATA ON BREATHING.						
Eupnea	500	12	6,000	300	240	0.80
Marked overventilation	1700	35	60,000	300	280	0.94*
Hyperpnea of exertion	1700	35	60,000	3000	2800	0.94

* CO_2 is being "washed out."

	Oxygen.		Carbon dioxide.	
	Vol. per 100 ml.	Pressure, mm. Hg.	Vol. per 100 ml.	Pressure, mm. Hg.
DATA ON RESPIRED AIR.				
Atmospheric air (inspired)	21.0	160	0.04	0.3
Expired air (eupnea)	16.0	120	4.00	30.0
Expired air (marked over-ventilation)	20.5	156	0.51	4.5
Expired air (exertion)	16.0	120	4.70	36.0
DATA ON ALVEOLAR AIR.				
Eupnea	13.2	97	5.25	40.0
Marked overventilation	19.0	145	0.65	5.0
Hyperpnea (exertion)	13.5	103	5.28	41.0
DATA ON BLOOD.*				
Eupnea:		tension		tension
Arterial	18.2	90	48.00	40.0
Venous	14.2	43	51.73	45.0
Overventilation:				
Arterial	18.5	140	46.30	38.0
Venous	14.5	41	50.00	43.0
Hyperpnea (exertion):				
Arterial	17.0	65	45.70	35.0
Venous	7.0	21	55.00	47.0

* Bloodflow in rest is assumed to be 7500 ml. per minute; in exertion, 30,000 mil. per minute.

Miscellaneous Respiratory Reflexes.—Almost any intense sensory stimulus modifies the breathing in some manner. The truly characteristic respiratory reflexes are evoked, however, by irritations

involving the respiratory tract itself (page 477). Coughing and sneezing are familiar examples. In these reflexes particularly vigorous forced expirations are evoked, with closure of the glottis followed by its sudden release. The sharp blast thus generated tends to expel the irritant either from the throat or the nasal passages, according to the direction given the air current by the muscles at the back of the throat. In rabbits and some other mammals irritating gases cause reflex closure of the nostrils. In ducks, and probably in other diving birds as well, application of water to the bill causes suspension of breathing movements. Laughing, crying, sighing and yawning are reactions in which the afferent basis is more complex than in the sharply-defined reflexes described above. The modifications of breathing concerned in voice production fall in the category of conditioned reflexes (page 723).

INTRAPULMONARY PRESSURE.

When the glottis is open and the chest stationary the pressure within the lungs (*intrapulmonary pressure*) is necessarily the same as atmospheric pressure. During inspiration, while the chest is in the act of enlarging, intrapulmonary pressure falls in accordance with the familiar law of the inverse relation of volume to pressure in gases. If the air passages are closed a strong effort of inspiration may lower intrapulmonary pressure as much as 80 mm. Hg. (Donders). If the air passages are open the actual fall in pressure is small (9 to 10 mm. H_2O), since air enters the lungs in response to the slightest pressure drop, and prevents a pronounced difference from developing. During expiration with open air passages intrapulmonary pressure rises just enough to force out the air that is expired (8 to 10 mm. H_2O). A strong expiratory effort with the air passages closed may raise intrapulmonary pressure 100 mm. Hg. or thereabouts above atmospheric.

Relation of Lung Growth to Chest Growth.—In the unborn infant the lungs contain no air, the alveoli and air passages being compressed in such a way that lung tissue is about as compact as the other soft tissues. The first breathing movements at birth cause air to enter the air spaces. After this once takes place the lungs cannot collapse so completely as to become entirely empty of air again. The small quantity permanently imprisoned is known as *minimal air*. (The lung of an infant that has never breathed will sink in water. After breathing has occurred the lung will float. This so-called *hydrostatic test* is of medico-legal importance.) During the first few days of the child's life the residual air (page 367) and the minimal air are practically identical in amount. In other words, the new-born child can expire so completely that its lungs are about as nearly collapsed as they can become. It is obvious

that when this happens the lung tissues are not distended with air and are therefore not at all on the stretch. Each inspiration, by causing air to enter the lungs, puts them on the stretch, the amount of stretch depending on the depth of the inspiration.

As the child grows its chest grows faster than its lungs. The inevitable result of this difference in rate of growth is that the lung walls are put permanently on the stretch. For they are continuously subject from within to the intrapulmonary pressure which is atmospheric or nearly atmospheric; much more than sufficient to keep the lungs in firm contact with the chest walls. By the time adult size is reached the utmost effort of expiration leaves the lungs with about a liter of air in them (page 367), and hence under some slight stretch. When the chest is in the resting position the tension amounts to 3 to 4 mm. Hg.

INTRATHORACIC PRESSURE.

The lungs are held in firm contact with the chest walls, as pointed out above, by the intrapulmonary pressure. They do not, however, press upon the chest walls or the other organs of the thorax with quite as much force as this, because their own elastic tension takes up a small part. The actual pressure of the lungs upon the chest walls and contents is called *intrathoracic* pressure. It equals the intrapulmonary pressure minus the elastic tension of the lungs. The elastic tension of the lungs varies with the state of expansion of the chest, being least in extreme expiration and greatest in extreme inspiration. In the latter position the tension may be as great as 30 mm. Hg.

The practical significance of intrathoracic pressure is in connection with the "aspiration of the thorax" (page 347). Whenever the air passages are open, so that intrapulmonary pressure is equal to atmospheric, the intrathoracic pressure is less than atmospheric. The great veins and large lymph ducts are, therefore, under a less compression in the thorax than elsewhere in the body, a situation favorable to the return of venous blood and lymph to the heart. The return is further favored by the rhythmic changes of intrathoracic pressure accompanying breathing movements (page 365). At the end of a quiet inspiration the intrathoracic pressure averages about 754 mm. Hg. (760–6), and at the end of a quiet expiration about 756 mm. Hg. (760–4). Even this small pumping action is probably of some significance, but much less than the action developed in deep breathing, in which intrathoracic pressure may drop as low as 730 mm. Hg. (760–30) in extreme inspiration, and rise to 758 or 759 mm. Hg. in extreme expiration.

When respiratory efforts are made with the air passages closed the variations in intrathoracic pressure follow those in intra-

pulmonary pressure (page 382), but are always lower than the latter by an amount determined by the position of the chest at the instant the air passages are closed. In any expiratory effort with closed glottis the intrapulmonary pressure rises above atmospheric, and usually far enough so that intrathoracic pressure also goes above atmospheric. The most striking effects are seen when the expiratory efforts are intense (violent coughing, defecation, parturition), when intrathoracic pressure may mount nearly to 860 mm. Hg. (page 382). The damming back of the blood in the large veins under these conditions has already been commented on (page 347). Sighing, yawning and voluntary deep breathing (in moderation) owe most of their physiological significance to the considerable changes in intrathoracic pressure induced by them.

Pneumothorax.—If the chest wall or parietal pleura is punctured, so that air under atmospheric pressure is admitted to the pleural cavity (only a potential cavity under normal conditions), the lung on the side of the puncture tends to collapse under the force of its elastic tension, now unbalanced, and if the opening is not closed promptly will collapse completely. The imprisonment of air in the pleural space constitutes *pneumothorax*. If the opening is closed the air in the pleural space will gradually be absorbed by the blood and the lung forced back to its normal position.

PRINCIPLES OF VENTILATION.

The air in a closed room inhabited by human beings undergoes a series of changes. The oxygen is depleted, the carbon dioxide and water vapor increase in concentration, the temperature rises, and smaller or larger quantities of volatile organic substances are introduced by evaporation of sweat and by exhalation from the alimentary tract. It is doubtful whether healthy lungs give off any other compounds than water and carbon dioxide, although the opinion that they also exhale toxic compounds has been widely held.

The primary disagreeable symptoms, chiefly headache and depression, that develop from breathing vitiated air are undoubtedly due to the effects of moisture and rising temperature. Ill effects due to the other factors are relatively so much slower in showing themselves that they are not likely to cause trouble if the ventilation is adequate in respect to these two. In fact it is doubtful whether in any place of ordinary human occupancy either the exhaustion of oxygen or the excessive accumulation of carbon dioxide is likely to attain a degree menacing to health; in the case of CO_2 about a 3 per cent concentration. Formerly, the ill nourishment and general poor vitality of slum dwellers have been attribued in large part to the constant breathing of air poisoned by organic effluvia. Recent

studies have raised a strong presumption, however, that lack of sunlight and vitamin-deficient food are more probably responsible.

In modern ventilation practice as applied to large buildings the same air is circulated repeatedly, being washed at each circuit, heated or cooled to a temperature of 65° to 70° F., freed of moisture in excess of a relative humidity of 50 to 60 per cent, and kept in continuous motion at a rate sufficient to deliver approximately 15 cubic feet per minute per person. A system of this kind implies the continuous intake of a relatively small proportion of fresh atmospheric air, ostensibly to replace air that escapes through fireplace flues, opened doors and the like, but serving incidentally to make good such oxygen depletion as would otherwise develop.

Summary.

Breathing is carried on by skeletal muscles, innervated by somatic motor nerves. The neuromuscular mechanism is susceptible to volitional and reflex excitation. It is also subject to spontaneous rhythmic excitation derived from the respiratory center in the medulla.

The respiratory center is assumed to be so constituted that when the hydrogen-ion concentration within its cells rises above a certain critical level nervous discharges are set up. The greater the acidity the more active the discharges.

The hydrogen-ion concentration of the respiratory center depends on the balance between acid production within the center, due to its own metabolism, and the escape of acid by diffusion from the center. The escape of acid depends on the CO_2 tension of the blood, which depends, in turn, on the balance between CO_2 production in the body as a whole, and escape of CO_2 from the blood into the alveolar air. In other words, the intensity of discharge of the respiratory center is conditioned by the CO_2 pressure of the alveolar air, other factors remaining constant.

The acid stimulation of the respiratory center is made effective as a means of inducing lung ventilation, by virtue of a nervous mechanism which is thrown into action with each inspiration. This mechanism, by suppressing the discharges of the center, permits passive lung deflation to occur in regular sequence with lung inflation. Eupnea and the deepened inspirations of hyperpnea are explained in terms of these interacting chemical and nervous influences.

To account for the faster rhythm often seen in hyperpnea a second nervous mechanism is postulated. This mechanism is assumed to become active whenever the lungs deflate from a position of greater inflation than usual; its effect is to stimulate the respiratory center to a prompter discharge than acid alone will induce. The afferent

pathways of both this and the mechanism for lung deflation are in the vagus nerves.

The forced expirations of dyspnea are interpreted to mean that at a second hydrogen-ion concentration, higher than that of inspiratory discharge, the respiratory center discharges impulses to the *expiratory* muscles. These are so timed as to reinforce the passive expirations.

In violent exertion the escape of CO_2 from the respiratory center is hindered and its acidity promptly rises to a point of intense discharge. The resultant increase in lung ventilation is sufficient to permit the uptake by the blood of as much oxygen as the tissues can utilize, and the giving off of as much CO_2 as they produce, without seriously changing the composition of alveolar air.

The hyperpnea of anoxemia is accounted for in part as due to a lessening of the percentage of oxyhemoglobin in the arterial blood. There is correspondingly less reduction to hemoglobin, and that part of the acid-carrying property of blood which depends on the change from HbO_2 to Hb is less effective. A second factor is thought to be an increase in acidity within the center, due to the incomplete reconversion of lactic acid to carbohydrate, the reconversion being dependent on accompanying oxidations.

In hemorrhage hyperpnea may develop as a result of the interference both with oxygen delivery to the respiratory center and with CO_2 removal from it. When pure oxygen at about 3 atmospheres' pressure is breathed the plasma may carry enough oxygen in solution to meet the needs of the tissues. The absence of reduction of HbO_2 to Hb lessens the acid-carrying capacity of the blood and so may induce hyperpnea.

In asphyxia the combination of anoxemia with failure to remove CO_2 leads to excessive acidity of the respiratory center with attendant extreme dyspnea, culminating in convulsions. Exhaustion of the respiratory center then sets in.

After the respiratory center becomes exhausted artificial respiration must be applied if restoration is to be obtained. The method of Schaefer is described.

Overventilation of the lungs has little effect on oxygen uptake by the blood. It does, however, reduce the CO_2 pressure of alveolar air below the normal level and so causes the gas to escape from the blood into the alveolar faster than it enters the blood from the tissues. The respiratory center thereupon becomes less acid and diminished breathing or apnea sets in.

The respiratory quotient is the ratio by volume of the carbon dioxide produced in metabolism to the amount of oxygen consumed. In normal breathing the respiratory quotient can be determined by estimations of the oxygen lost from inspired air and the carbon dioxide given off in expired air. In overventilation, and in a period

immediately following, the CO_2 content of expired air does not equal the CO_2 output from the tissues, since the CO_2 tension of the blood is changing. Determinations of the respiratory quotient during these periods are not, therefore, representative of the metabolic state of the body.

Numerous respiratory reflexes exist. The most significant of these are due to irritations arising in the respiratory tract and are adaptive in character.

Intrapulmonary pressure equals atmospheric when the chest is stationary and the air passages open. During inspiration intrapulmonary pressure falls, slightly if the air passages are open, 80 mm. Hg. or so if closed. During expirations intrapulmonary pressure rises, again slightly if the air passages are open; to 100 mm. Hg. when closed.

Before birth the lungs contain no air. They fill the available chest space without being stretched. As the child grows the chest grows faster than the lungs, with the result that the lungs, which continue to fill the available space, are in a state of stretch. The stretching force is intrapulmonary pressure.

The pressure of the lungs upon the chest walls and chest contents is *intrathoracic pressure*. It equals intrapulmonary pressure minus the elastic tension of the stretched lungs. It changes rhythmically with breathing, the change becoming marked in deep breathing. The effects, designated as the "aspiration of the thorax," are mainly on the flow of venous blood and lymph.

Puncture of the pleural cavity results in collapse of the lung. The presence of air in the pleural space constitutes *pneumothorax*. If the opening is closed the air will ultimately be absorbed by the blood.

Practical ventilation methods, as applied to large buildings, are based on the fact that the disagreeable symptoms experienced in closed rooms are primarily due to rising temperature and excessive humidity. If these factors are kept within bounds the other potential harmful factors, oxygen depletion and CO_2 accumulation, are not likely to become significant.

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CHAPTER XXIV.

THE MECHANISM OF DIGESTION: DIGESTION IN MOUTH AND STOMACH.

FUNCTIONS OF THE DIGESTIVE APPARATUS.

In the capillaries of the alimentary tract the blood is renewed in respect to water (page 157), salts (page 172), vitamins (page 193) and nutrients (page 175). So far as water, salts and vitamins are concerned the essential mechanism is the thin lining membrane of the intestinal tract, backed by abundant capillaries. The conditions of absorption are the presence in the intestinal tract of adequate quantities of the substances concerned and a sufficient flow of blood through the capillaries.

The nutrients present a more complex problem; proteins must be decomposed to amino-acids before entering the blood stream (page 181); polysaccharides and disaccharides must be converted to glucose (page 176); fats must be transported across a watery membrane and made suspensible in watery plasma.

THE DIGESTIVE PROCESS.

To prepare the nutrients a series of hydrolytic cleavages takes place (page 52). These are catalyzed by enzymes (page 53), which are to a considerable extent specific in their action. The digestive process as a whole involves, therefore, the presence of several enzymes (probably eight or nine in all) and a corresponding wealth of gland action (page 134).

In the majority of invertebrates and in all vertebrates the digestive process consists in passing the nutrient-containing food mass along an alimentary tube, into which the ducts of enzyme-secreting glands open at various levels. The food mass is propelled by contractions of smooth muscle (ciliary motion in some invertebrates) under the control of the autonomic nervous system, but subject also to chemical and mechanical influences brought to bear locally. The glands which produce the digestive enzymes pour out their secretions as the result of stimulation either through the autonomic nervous system, or by means of hormones, or both. Proper functioning of the digestive mechanism depends on a close coördination of muscular and glandular action. The rate at which the food mass is moved along each part of the tube must harmonize with

the time required for the enzymes present there to do their work. The secretion of individual enzymes must be timed, in turn, to agree with the arrival of the food mass at their level, and the quantity of secretion must be adjusted in some measure to the amount of material to be digested.

To emphasize this harmony of action, and the mechanism by which it is secured, the method of presentation here adopted is that of following an ordinary meal through the alimentary tract, describing at each stage the interacting muscular, nervous, glandular and enzyme functions by which the digestive process is carried on.

Character of an Ordinary Meal.—An ordinary, fairly heavy meal weighs 500 to 600 gm., of which one-half or more is water; 5 to 15 per cent of the balance indigestible material (frequently spoken of as *roughage*); about 2 per cent salts; a minute undetermined quantity vitamins and flavor-lending components; the remainder a mixture of starches, sugars, animal and vegetable proteins and animal and vegetable fats.

MASTICATION.

The first process is that of mastication, by which each mouthful of food is reduced more or less completely to a pasty consistency. The objects are obviously to break up the food masses, so as to present as large a surface as possible to the action of the digestive enzymes and to secure thorough admixture with saliva. In addition to the actual chewing motions, which are carried on by the muscles that move the lower jaw, coördinated motions of the tongue and cheeks occur by which the food mass is manipulated into position for chewing and also gradually worked toward the back of the mouth in readiness for swallowing. The muscles are all of the skeletal type, innervated by somatic motor nerves. The act of mastication is accordingly either volitional or reflex. Volition may enter to a slight extent, but in the main the chewing of the food falls in the category of conditioned reflexes (page 723).

Large scale studies on school children have brought out the important fact that inadequate mastication, whether due to poor teeth or bad eating habits, is an important contributary factor in malnutrition.

THE SALIVARY GLANDS.

In man there are three pairs of salivary glands. the parotids, submaxillaries and sublinguals. The duct of the parotid is Stenson's duct, opening into the mouth cavity opposite the upper second molar. To guard against the copious secretion poured out through this duct dentists place rolls of cotton between the upper jaw and the cheek. The submaxillary opens by Wharton's duct into the mouth cavity underneath the tongue. The several small ducts of the sublingual also open underneath the tongue.

The bloodvessels of the salivary glands have both vaso-dilator (parasympathetic) and vaso-constrictor (sympathetic) innervation (page 131). The cells of the glands have also direct secretory innervation (page 136); in dogs by way of the parasympathetic system; in cats apparently by way both of the parasympathetic and the sympathetic. The course of the secretory fibers in man is not known. An interesting anatomical detail is that the parasympathetic fibers to the submaxillary and sublingual glands extend across the cavity of the middle ear as components of the *chorda tympani* nerve.

Stimuli to Salivary Secretion.—Stimulation of the chorda tympani nerve (parasympathetic) in experimental animals causes an abundant out-pouring of saliva from the submaxillary and sublingual glands. The same stimulus causes also pronounced vaso-dilation in these glands. According to the picture of salivary gland action already presented (page 136) the secretory stimulus proper is thought of as making the outer faces of the gland cells permeable to the various components of the secretion, and thus as setting in motion the series of processes which make up the act of secretion. The accompanying vaso-dilation brings about a copious blood flow through the gland. This copious blood flow is obviously favorable to the formation of an abundant secretion.

Stimulation of the sympathetic innervation (the cervical sympathetic) causes vaso-constriction in the vessels of the gland, and in dogs either a complete suspension of whatever secretion may have been in progress or its reduction to a small quantity of thick and viscid fluid. This is explained as due in part to the absence of secretory stimulation, and in part to the shutting off of the blood supply. There is no evidence of specific *inhibitory* fibers acting to decrease the permeability of the gland cells. In cats sympathetic stimulation results in a copious flow of saliva. Apparently the vaso-constriction is not marked enough to prevent the secretory fibers from producing their typical effect.

Salivary Reflexes.—In the intact body the salivary glands are excited to secrete either through reflex action or through the operation of affective (*i. e.*, emotional) states. The reflexes originate for the most part in receptors within the buccal cavity. These receptors may be stimulated mechanically, as by rubbing the tongue against the walls of the cavity or by chewing a rubber band or a piece of wax. The result of such stimulation is an abundant outpouring of saliva. Introduction of substances possessing either taste or flavor (page 543) into the mouth is followed typically by an even more copious secretion.

The parotid glands in man produce a watery secretion rich in enzyme but poor in mucin (page 139) and much more dilute than blood (specific gravity, 1.002 to 1.008, as compared with 1.030 for

blood plasma). The secretion of the submaxillary and sublingual glands is rich in both enzyme and mucin, and is accordingly much more viscid than the parotid secretion. Mechanical stimuli appear to excite the parotid glands more particularly, while chemical stimuli throw the submaxillary and sublingual glands also into vigorous action. Pavlov and others have described some remarkably close adjustments between the special character of the stimulus and the composition of the resultant saliva. Thus both acid and meat powder in the mouth arouse an abundant secretion, but that induced by meat powder contains a much higher percentage of solids than that induced by acid. How these selective effects are brought about has not been satisfactorily explained in accordance with modern views as to the nature of the nerve impulse.

The Relation of Affective States to Salivary Secretion.—It is well known that the "mouth waters" in connection with the thought of savory food, and also in less agreeable circumstances in connection with sensations of nausea (page 407). These reactions are attributed to characteristic out-pourings of impulses over the parasympathetic autonomic system, aroused in connection with particular affective states. In man such affective states as are attended by out-pouring of impulses over the sympathetic system (fright, anger embarrassment; page 735) cause suppression of salivary secretion. It is interesting that in cats spitting is one of the reactions to fright or anger, and in these same animals, contrary to the general rule, the sympathetic system appears to carry secretory fibers to the salivary glands.

Functions of Saliva.—The mechanical action of the tongue and other mouth parts on the buccal receptors suffices to evoke, chiefly from the parotids, a sufficient secretion to keep the mouth, throat and esophagus adequately moistened all the time. This is an important factor in the prevention of thirst (page 159). But when food is taken into the mouth and chewed all the factors favorable to excitation of salivary secretion, mechanical, chemical and psychic, are thrown simultaneously into action, and an abundant out-pouring takes place from all the glands. The total twenty-four-hour flow of saliva in man has been estimated at over 1 liter. The between-meal secretion probably averages not far from 0.5 ml. per minute, or 720 ml. per twenty-four hours. Assuming a total secretion of 1200 ml. the additional secretion due to eating is about 500 ml. If the total time devoted to chewing food during the day is one hour, this implies about a sixteen-fold increase in secretory activity. The saliva secreted during eating serves two important functions. One is simply that of adding enough water to the food mass so that it takes on the proper pasty consistency; the other is the introduction of the enzyme *ptyalin*, or *salivary diastase*.

Action of Salivary Diastase.—Salivary diastase catalyzes the hydrolysis of starch. The first steps in the decomposition of the complex molecule convert starch into *dextrins*, a series of polysaccharides having the same empirical formula as starch itself, *i. e.*, $(C_6H_{10}O_5)_n$. The final stage in the hydrolysis results in formation of the disaccharide, *maltose*, whose empirical formula is $C_{12}H_{22}O_{11}$. The range of hydrogen-ion concentration within which salivary diastase functions is near the neutral point, extending only a short distance from it in either direction (saliva is said to range from pH 6.6 to pH 7.1). Outside its range the enzyme is inactive (page 54). The fact that gastric juice is decidedly acid (page 398) led observers to minimize the significance of salivary digestion, since it is obvious that food is swallowed and enters the stomach before the action has time to proceed far. But when it was shown that food in the fundus may not come into contact with the acid gastric juice for an hour or more the importance of salivary digestion was reëstablished. It should be noted here that maltose is not utilizable by the body as such. A further digestive action (in the small intestine; page 419) is necessary to reduce the maltose to glucose.

DEGLUTITION.

The act of swallowing can be performed readily if there is saliva or moist food in the back part of the mouth. It is performed with difficulty or not at all if that region is dry. Between meals the function of swallowing is to convey saliva to the pharynx and esophagus in order to moisten them, and incidentally to prevent the undue accumulation of saliva in the mouth. As a phase in the digestive process the act begins when a bolus of chewed food is gathered at the back of the mouth. The process is described as occurring in three stages. The first is the squeezing of the bolus through the isthmus of the fauces, mainly by the elevation of the tongue against the palate, beginning from in front backward. This stage may be initiated volitionally, although it is usually performed unconsciously, in which case it is to be looked on as a reflex. The succeeding stages are definitely reflex in initiation and consummation.

In the second stage contractions of various muscles in the throat and back part of the mouth close the glottis and the posterior nares, in other words, all the outlets from the pharynx except that by way of the esophagus. A sharp contraction of the mylohyoid muscle in the floor of the mouth then shoots the bolus rapidly across the pharynx into the esophagus. The time required does not exceed one second. The action involves accurately coördinated contractions on the part of a number of skeletal muscles, and ranks, therefore, as a highly complicated reflex (page 127). The receptors whose stimulation starts the reflex are located in the wall

of the pharynx, in slightly different areas in different species of mammals. In the normal course of events the impact upon these receptors of the material passed through the isthmus of the fauces in the first stage is the adequate stimulus for initiating the second stage.

The impulse given the food mass by the contraction of the mylohyoid muscle is sufficient, provided the bolus is watery enough, to shoot it the whole length of the esophagus to the sphincter of the cardia, a ring of smooth muscle guarding the entrance to the stomach from the esophagus. The passage occupies about one-tenth second. The third stage of deglutition, which is the stage in which the esophagus is involved, gets under way immediately upon the entrance of the food mass into the esophagus and runs its course whether the bolus is shot at once to the cardiac sphincter or not. It consists of a progressing wave of contraction of circular muscle fibers (technically known as *peristalsis*), which starts at the upper end of the esophagus and moves along it, arriving at the sphincter in about six seconds. The upper portion of the wall of the esophagus contains mostly skeletal muscle fibers. These are replaced more and more by smooth muscle fibers as the stomach is approached, until at the lower end only smooth muscles remain. The peristaltic wave in the skeletal muscle part of the esophagus is a complex coördinated reflex initiated apparently by the same stimulus in the pharynx as evokes the second stage described above. The motor nerve fibers pass by way of the vagus trunks and their esophageal branches to the esophageal muscle fibers. The onward movement of the wave depends on the stimulation of successive rings of muscle fibers in order. To account for the accurate coördination of nervous discharge implied in this action a *deglutition center* in the medulla is postulated, although it must be admitted that direct evidence of the existence of such a center is wanting. The peristaltic wave propels to the stomach any bolus too solid or too adhesive to be shot the length of the esophagus.

The Passage of the Cardiac Sphincter.—The lower part of the esophagus, consisting of smooth muscle, functions in a particular way in connection with the cardiac sphincter to introduce the boluses of swallowed food into the stomach. Its action is, therefore, dealt with in connection with the latter process. To understand the mechanism by which food enters the stomach it is necessary first to become acquainted with some facts about that organ. The stomach is a pouch of smooth muscle which receives excitatory innervation from the parasympathetic system and inhibitory innervation from the sympathetic system. By virtue of the nerve plexuses in its wall, it also shows intrinsic contractions, independently of influences from the central nervous system. Spasmodic contractions of this nature stimulate receptors in the stomach wall, giving rise to sensations of *hunger*.

For a short period after the stomach has emptied itself the organ may be in a state of low tonus (page 93), with its walls flabby, and with the cardiac sphincter probably as relaxed as any other part of the musculature. It appears that except at such brief periods the tendency is for more or less tonus to be present. This implies that the walls are putting the contents under pressure. Even when the stomach is said to be empty it contains 10 to 200 ml. of fluid, averaging 30 to 50 ml. (Carlson), including some gastric juice, some swallowed saliva, often some fluid regurgitated from the duodenum, and, at its uppermost point, a bubble of swallowed air. The pressure of the stomach walls would tend to force these contents back into the esophagus were it not for the fact that whenever the stomach as a whole goes into tonus the cardiac sphincter tightens also. Regurgitation is thus prevented, except that occasionally the sphincter relaxes for some unknown reason, permitting eructation of some of the swallowed air, or even partial regurgitation of some of the liquid contents, giving rise to the sensations known as "heart burn." When the sphincter is in full tonus it is able to withstand a pressure from within the stomach of nearly 20 mm. Hg.

Food that is swallowed must pass the barrier of the cardiac sphincter, and must also enter a space which is under the pressure of the stomach wall. These facts imply either that swallowing is forcible enough to overcome the double resistance, or that there is an adjustment whereby the resistance is lessened as the food is swallowed. The latter situation is what actually prevails. The mechanism by which it is brought about is now to be described.

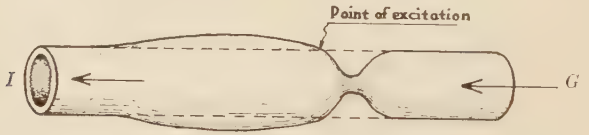

FIG. 42.—Diagram to illustrate action of the myenteric reflex. *G*, gastric, and *I*, iliac end of intestinal segment.

The Myenteric Reflex and the Entry of Food into the Stomach.—Some years ago the important discovery was made (Bayliss and Starling) that in certain parts of the alimentary tract, notably the lower (smooth muscle) end of the esophagus and the entire small intestine, peristaltic movement includes more than a simple advancing wave of contraction. Directly in front of the contraction wave there moves also an advancing wave of relaxation (Fig. 42). This combination of a wave of relaxation preceding a wave of contraction was found to depend on the integrity of the longer connecting nerve fibers of the myenteric plexus, and was designated by Cannon

the *myenteric reflex* to signalize its nervous background, although it is not a reflex in the sense that the central nervous system is involved (page 120). It is through the operation of this reflex in the esophagus that food gains entry to the stomach against the opposing back pressure. Each wave of contraction sweeping down the esophagus in the third stage of deglutition acts in effect as an advancing sphincter. Ahead of this advancing sphincter, as it traverses the smooth muscle portion of the esophagus, moves an area of relaxation. When the area of relaxation arrives at the cardia it involves the true sphincter, which accordingly relaxes. Any bolus that may be in the esophagus just above the sphincter is then pressed upon by the advancing wave of contraction, but not opposed by back pressure on the part of the sphincter. It is, therefore, forced on into the stomach.

An interesting fact in this connection is that the third stage of deglutition is inhibited and dies out if another first stage is initiated before the peristaltic wave reaches the cardiac sphincter. The result is that if swallowing movements are made in rapid succession, as in drinking a glass of water, the material swallowed accumulates in the esophagus until the final swallowing movement is made, when the third stage is left free to run its course, and the entire accumulation is passed on into the stomach.

THE DISPOSITION OF FOOD IN THE STOMACH.

The empty stomach, when in fairly strong tonus, as it is particularly likely to be when food is about to be eaten has a tubular form, quite different from the postmortem shape usually pictured. As observed with the aid of roentgen-rays (see below) the outline is much as shown in Fig. 43, except that the empty stomach is even narrower than when it contains some food, which is the condition represented in the figure. The sharp bend shown at the level of the incisura is characteristic of the full stomach. When the organ is empty the pyloric valve is said to be at the lowest point.

As food enters the stomach in the manner just described the walls of the organ adjust their tonus so that the pressure remains uniform (subject to rhythmic tonus waves usually present) while the capacity of the organ increases. This is what is meant by the statement that "the stomach fits the food" (page 93). Successive boluses force the food already in the stomach further and further along the greater curvature, and in such a manner that the food swallowed earlier is in close contact with the walls, while that swallowed later is imbedded in the food mass and thus kept from contact with the walls. This stratification of the food was well shown in an experiment of Grützner, who fed rats and other

animals food of different colors, and on killing the animals found the food stratified in the order of its feeding (Fig. 44).

The Churning of Food in the Stomach.—Most of our detailed knowledge of the movement of food into, through, and out of the stomach has been derived from roentgen-ray observations of the behavior of food masses made opaque by addition of bismuth subnitrate.

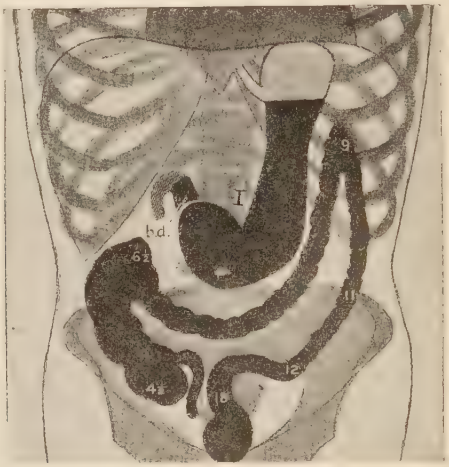

Fig. 43.—Roentgen-ray picture of stomach, duodenal bulb and large intestine in man. *b.d.*, duodenal bulb; *I*, incisura angularis. (From Hurst.) (Howell's Physiology, W. B. Saunders Company, Publishers.)

Fig. 44.—Stratification of food in stomach. Black indicates food first swallowed; vertical shading, second portion; horizontal shading, last portion. (Gruetzner.) (Howell's Physiology, W. B. Saunders Company, Publishers.)

Cannon was one of the first to use the method; his observations, mainly on cats, have been supplemented and extended by other investigators, working on human beings.

The stomach is subdivided structurally and functionally into the *fundus* and the *antrum pylori* or pylorus. The line of division between the two regions is indicated by the incisura angularis, a fissure on the lesser curvature (Fig. 43). The portion of the fundus near the esophagus is known as the cardiac portion. The function

of the fundus is mainly to serve as a reservoir, so that a fairly large quantity of food can be taken at a single meal.

The churning movements consist of peristaltic waves originating in the middle third of the stomach and moving toward and along the pylorus, dying out as they reach the *pyloric sphincter*, a ring of smooth muscle that guards the exit from the stomach as the cardiac sphincter guards the entrance into it. The myenteric reflex (page 394) does not govern these waves, as is shown by the fact that they follow one another in close succession, an arrangement that would not be possible if each wave of contraction were preceded by a wave of relaxation. (Cannon designates this type of movement *katastalsis*, to distinguish it from peristalsis governed by the myenteric reflex, which he calls *diastalsis*.)

The form of individual waves is complicated by the fact that the portion of the stomach over which they pass shows rhythmic tonus changes. Each period of increase and decrease in tone makes up a so-called *gastric cycle*, lasting about two to three seconds. At the beginning of each gastric cycle, namely, at each period of increase in tone, a peristaltic wave is set moving along the stomach from the point of origin. The speed at which the peristaltic waves travel determines how many of them shall be present at once. The rate of progress most frequently seen is one that makes each wave take about ten seconds to run its course. When this rate prevails four waves may be present at once, and the individual waves will become larger or smaller as the gastric cycles proceed from one phase of tone to another. In other, less common, types of gastric motility the rate of progress is more rapid, and three, two, or even only one wave may be present at once. Whatever the rate, a wave arrives at the pyloric valve every two to three seconds.

The waves tend to crowd the food in the part of the stomach over which they pass into the pylorus and up to the pyloric sphincter. In the event that the sphincter fails to yield and to allow food to pass on into the duodenum an eddy current is set up along the axis of the stomach. During this action gastric juice is being added to the food. The fundus is all the time keeping up pressure on its contents, so that as fast as any *chyme* (page 411) escapes into the duodenum it is replaced by material from the fundus. Meanwhile the contents of the fundus, except in the prepyloric region (next page), retain the hydrogen-ion concentration they had when swallowed, and so salivary digestion goes on uninterrupted.

GASTRIC JUICE.

The gastric glands are tubular glands incorporated in the stomach mucosa. Their secretion, known as *gastric juice*, is essentially a very dilute saline solution (specific gravity about 1.003) containing

hydrochloric acid and two enzymes, *pepsin* and *rennin*. (Lipase is said to be formed also, but it is destroyed promptly by the HCl, hence is not present in functional juice.) Pepsin is a proteolytic (protein-hydrolyzing) enzyme; rennin a milk-clotting enzyme. A very curious fact about rennin is that it is present in the gastric juice of the lower vertebrates, including fish and amphibia, whose diet never includes milk, and reptiles and birds that take it only incidentally if at all, as well as in mammals for whom it is essential.

Pepsin appears to be secreted in inactive form, as pepsinogen, and activated by contact with hydrochloric acid. The merit of this arrangement would be in fending off the tendency of the pepsin to digest the proteins of the cells that secrete gastric juice. The enzyme hydrolyzes proteins, not by splitting amino-acids off one by one, nor by causing the molecules to break up into their ultimate amino-acid constituents, but by breaking the huge protein molecules into polypeptides, *i. e.*, groups of amino-acids. These polypeptides are of varying degrees of complexity. The first to be formed are *syntonins*. (These compounds, known also as acid albumins, are probably formed through the action of HCl, rather than through the action of pepsin.) Next in order are the proteoses; last and simplest are the *peptones*, still complex polypeptides, which are the end-products of peptic digestion as it occurs in the body. It will be noted that pepsin is like salivary diastase in that its action is only partial. Further digestion of peptones is necessary, just as is further digestion of maltose (page 392).

Pepsin acts only in an acid medium. The optimum hydrogen-ion concentration is stated to be at pH 1.6 or thereabouts. This hydrogen-ion concentration is established by the secretion of hydrochloric acid (page 141). In pure gastric juice the acidity is somewhat above the optimum for pepsin, being about pH 1.3. The presence of saliva and of digesting food reduces the hydrogen-ion concentration, under normal conditions, to a point near the optimum.

The gastric glands contain two kinds of cells, the chief cells and the parietal cells. The former are thought to secrete enzymes and the latter hydrochloric acid. Chief-cell-containing glands are scattered pretty generally over the stomach, although more abundant in the fundus than in the pyloric region. (Many investigators doubt that the pyloric secretion contains true pepsin.) Parietal-cell-containing glands are confined rather strictly to the region between the middle of the fundus and the beginning of the pylorus, the so-called *prepyloric region*. From this distribution it follows that food in contact with the fundic wall in any part may become more or less impregnated with pepsin-containing juice, but the hydrogen-ion concentration essential to proteolytic digestion is established only in the region of active churning.

The Secretion of Gastric Juice.— One of the most fascinating chapters of physiology is that dealing with the growth of our knowledge of the control of gastric secretion. The presence of an irritating juice in the stomach has been known, of course, from time immemorial. During the eighteenth century various observers, among them Reaumer, Stevens and Spallanzani, obtained more or less pure gastric juice from birds and mammals, and from human beings, and showed that the juice would dissolve meat outside the body. Beginning with 1825, Beaumont made his famous series of investigations on Alexis St. Martin, the French Canadian voyager, who was left, after a gun-shot wound in the abdomen, with a permanent gastric fistula. The unique opportunity thus afforded for observing directly what goes on in the stomach was seized by Dr. Beaumont, and resulted in extensive and important additions to our knowledge of the digestive process.

FIG. 45.—Isolated stomach pouch, prepared by the method of Haidenhain. *a a*, the abdominal wall into which the isolated pouch, *S*, opens. (Pavlov.) (Howell's Physiology, W. B. Saunders Company, Publishers.)

Following Beaumont's work the use of gastric fistulas artificially established has become standard both as a means of obtaining gastric juice from experimental animals and of nourishing human beings who have suffered occlusion of the esophagus from one cause or another.

Heidenhain modified the procedure by setting aside a selected portion of the stomach as an isolated sac, with its own fistulous opening to the exterior (Fig. 45). The advantage of this modification is that it enables the observer to obtain uncontaminated gastric juice at the same time that normal digestion is going on in the remainder of the stomach.

The modern conception of the control of gastric secretion dates from the work of Pavlov (beginning a few years prior to 1900). This investigator improved the Heidenhain stomach-pouch operation so that the nerve supply and blood supply of the pouch were undisturbed; he also performed the additional operation (in dogs) of dividing the esophagus in the neck and bringing both cut ends to the surface in a double esophageal fistula. Animals thus treated made prompt and complete recovery and were entirely normal, except that all food eaten and swallowed was at once discharged to the outside through the upper fistula (Fig. 46), and food would reach the stomach only if introduced again into the lower. There was also a slight reduction in stomach surface available for digesting food, on account of the setting aside of a portion as a Heidenhain pouch.

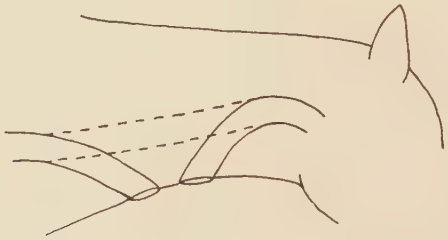

FIG. 46.—Double esophageal fistula, as prepared by Pavlov.

The significance of the Pavlov procedure is that it distinguishes between effects induced as the result of, or in connection with, the chewing and swallowing of food, and effects due to the presence of food in the stomach. The findings of Pavlov may be summarized briefly as follows: When a hungry animal, prepared as above, is fed a "fictitious meal," *i. e.*, given food to chew and swallow, but none into its stomach, it eats with unabated enjoyment for an indefinite period (presumably until overcome by fatigue), and during the whole time of eating, after a preliminary latent period of four or five minutes, pours forth a copious secretion of gastric juice. This is known as the "appetite secretion." It is aroused by nervous impulses which travel to the stomach over the vagus nerves. The essential condition is the *eating of food with appetite*, and implies, therefore, a definite psychic state, reinforced by the mechanical and chemical stimuli which attend the eating process. Tasteless food may be chewed and swallowed more or less indifferently, apparently as a matter of habit as much as anything, without display of eagerness, and without the evocation of augmented quantities of juice. Furthermore, affective states attended by sympathetic dis-

charges, such as anger and fright (page 735), bring about prompt suppression of the appetite secretion. In some animals it is apparently possible to evoke an appetite secretion merely through the smell and sight of food; a phenomenon analogous to the "watering of the mouth." But this reaction is less certain than the one in which actual satisfaction of appetite enters. The reaction as a whole falls in the category of conditioned reflexes (page 723).

Supplementary Gastric Secretion.—Carlson has shown that the gastric glands are not inactive between meals, but secrete continuously at the rate of 2 to 60 ml. per hour, averaging about 30 ml. per hour. Simple water drinking increases the rate somewhat. During eating the rate is much augmented, rising to as much as 3.5 ml. per minute. The total secretion for a meal may amount to 700 ml. or more. The augmentation in its early stages is obviously due to the appetite secretion described above. But the whole increase cannot be thus accounted for. The appetite secretion evoked by a fictitious meal comes to an end in man within fifteen to twenty minutes after discontinuing the feeding. When food enters the stomach, on the other hand, augmented gastric secretion may continue until the organ empties itself, a matter often of six hours or more. The total amount of juice poured out in digesting a meal is thus much greater than the appetite secretion. Carlson has shown, furthermore, that under suitable conditions an abundant outflow of gastric juice may be called forth quite independently of any appetite secretion whatsoever.

The mechanism by which the glands are stimulated to pour forth this supplementary secretion is in doubt. It appears to depend on the presence either of partially digested proteins, meat extracts or milk in the stomach. It is known, furthermore, not to be a reflex through the central nervous system, since it continues after the nervous connections with the brain and cord are severed. The three possibilities that suggest themselves are: (*a*) A local nervous reaction to *mechanical* stimulus resulting from the presence of food in the stomach; (*b*) a local reaction to *chemical* stimulation arising also from food in the stomach; (*c*) a reaction to a *hormone* which reaches the gland cells through the blood.

The first alternative has apparently been made untenable by the finding that only the materials mentioned above seem able to arouse the supplementary secretion. Others, with presumably as positive mechanical action as these, are ineffective, so far as experiments have yet shown. The second alternative has been neither positively proved nor disproved. It has attracted relatively little attention on account of the wide acceptance which a theory based on the third alternative has received until recently.

This theory, which assumes that the supplementary secretion is due to stimulation by a hormone, is based on a series of experi-

ments by Edkins, in which acid extracts of pyloric mucous membrane, or extracts made by boiling the mucosa with peptone solution, were injected into the blood and found to cause increased secretion of gastric juice. These experiments were interpreted to mean that a hormone is produced normally by the cells of the pyloric mucosa, presumably as the result of a reaction between a constituent of the cells of the mucosa and some substance contributed by the food, which hormone is carried to the gland cells in the blood stream and stimulates them to secrete. The name *gastrin* was assigned to the hormone.

The first definite cloud on this theory was cast by the discovery that hydrochloric acid extracts of a wide variety of plant and animal tissues stimulate the gastric glands to activity. We are obviously dealing with a substance of quite general occurrence, and while this substance may act as a hormone in accordance with the theory as outlined, better proof that it does so is demanded than the experiments of Edkins afford. Attempts to obtain this additional proof by eliciting secretion from the glands of the fundus as the result of applying meat extracts, peptones and other food substances to the pyloric mucosa have been successful in the hands of one investigator (Gross) but have given negative results in the hands of another (Ivy). It is obvious that the gastrin theory cannot be either accepted or rejected finally until still further evidence is brought forth.

Pavlov and his co-workers found that the quantity of gastric juice secreted is proportional both to the amount of food eaten and to its palatability. This relationship is easy to account for on two grounds: (1) The more appetizing the food the more copious will be the appetite secretion; (2) the larger the quantity of food the more potent or more prolonged will be its action in evoking the supplementary secretion. The same workers state that different kinds of food produce secretions that differ in acidity or in percentage of pepsin. Juice produced by bread has one character, by meat a second and by milk still a third. Carlson is inclined to the view that these differences are due to differences in rate of secretion. A juice that is poured out rapidly is apparently more acid than one secreted slowly, but contains a lower concentration of pepsin. How the character of the food influences the rate of gastric secretion remains to be determined.

Measurement of Peptic Action.—Various methods have been devised for studying the influence of such factors as temperature, hydrogen-ion concentration, quantity of enzyme, etc., on the rate of action of pepsin. The one generally used is that of Mett. Raw white of egg is sucked up into small glass tubes and coagulated there by dropping the tubes for five minutes into water at 95° C. After the tubes have cooled they are cut up into lengths of 10 to 15 mm.

These short tubes are placed in the various test solutions, and the digestive action measured by the length of the section of albumin dissolved in a given time.

THE EMPTYING OF THE STOMACH.

The outlet from the stomach into the duodenum is guarded by the pyloric sphincter. This sphincter is contracted all the time except for intermittent brief relaxations by which food is permitted to pass on into the duodenum. It appears that the sphincter does not hold against water, raw egg-white or other materials similar to egg-white in consistency. With these exceptions, a definite act of relaxation is necessary for the passage of substances onward.

Following the eating of a meal there is a variable period, ranging from five or ten minutes up to one-half hour or more, during which the steady procession of peristaltic waves coursing over the stomach from the middle of the organ crowds the food up against the sphincter, but forces none through (page 397). Thereafter the sphincter relaxes at intervals sufficiently to let a small bolus through and immediately contracts again. This momentary relaxation is repeated from time to time until the stomach is entirely emptied, a period of four to six hours ordinarily. The details of the action are described differently by different observers, indicating either considerable individual variation or that the procedures followed in obtaining the observations influence the behavior of the stomach. Cannon found in cats a definite relationship between the character of the food and rate of emptying. Carbohydrates began to be discharged much sooner and were all evacuated more quickly than proteins. Fats delayed the action still more than proteins. These relationships have been stated by some observers to apply to man, but others have found that one foodstuff leaves the human stomach about as quickly as another.

Cannon showed that the pyloric sphincter is subject to the myenteric reflex (page 394), functioning in this respect rather as the beginning of the intestine than as the termination of the stomach, since the latter organ, as already pointed out (page 397), does not display the reflex. A cardinal feature of the myenteric reflex, not yet described, is that it can be elicited by direct stimulation in regions subject to it. Pinching a spot in the intestine with forceps, for example, causes the circular muscle layer contiguous to the spot and *anterior to it* to contract strongly, and at the same time a more extensive area, *immediately posterior to the point of stimulation*, to relax (Fig. 42).

The pyloric sphincter is posterior to all points in the stomach. It follows that any stimulus brought to bear on the sphincter from the stomach side should cause it to relax. Conversely, any stimulus

brought to bear from the intestinal side should cause the sphincter to contract. Experiments on the myenteric reflex in the intestine indicate that if one and the same group of muscle fibers is stimulated simultaneously from before and behind, tending to evoke both relaxation and contraction at the same time, the stimulus tending to cause contraction dominates. If this finding holds for the pyloric sphincter it will remain contracted so long as stimuli play upon it from the intestine, no matter what influences may be acting from within the stomach.

It is conceivable that either mechanical or chemical stimuli may be effective to operate the sphincter. Every arrival of a peristaltic wave subjects it to increased pressure. This pressure might act as a mechanical stimulus, causing the sphincter to relax, provided no counteracting stimulation were present in the intestine at the time. Various observers have reported that the passage of food through the sphincter coincides with the arrival there of peristaltic waves. There is evidence, also, in support of the possibility that the portion of the duodenum immediately adjacent to the pylorus (the so-called *duodenal cap;* Fig. 43) retains discharged material within itself or passes it on in accordance with a rhythm of its own. The back pressure of substances in the cap may act as a stimulus to keep the sphincter contracted, and the emptying of the cap, by removing this stimulus, may open the way for the sphincter to relax under the mechanical stimulus of an arriving peristaltic wave, and to discharge another bolus.

Pavlov, and more particularly Cannon, have supported the view that the control of the sphincter is predominantly chemical. In fact, they go further and assign the control definitely to the hydrogen-ion concentration of the pyloric contents. Cannon showed by direct experiment in cats that relaxation of the sphincter can be induced by making the stomach contents acid. Serdjukow showed that acid in the duodenum keeps the sphincter firmly closed. On the basis of these and other corroborative observations, Cannon pictures the control of the sphincter briefly as follows: The acid poured out at the beginning of gastric digestion mixes with the food, and is either neutralized by the saliva or absorbed by the buffer action of the proteins, hence does not raise the hydrogen-ion concentration. In course of time, however, and sooner with carbohydrates than with proteins, the hydrogen-ion concentration rises to a point at which the pyloric sphincter is stimulated to relax. This marks the moment at which the first bolus is discharged into the intestine. As the bolus passes into the intestine it carries its acid with it. This acid stimulates the sphincter from the intestinal side. It accordingly closes promptly, in spite of the fact that there is still acid in the stomach tending to produce relaxation. The sphincter then remains shut until the acid in the duodenum is

neutralized by the pancreatic juice and bile, when it is set free to relax again under the influence of stomach acidity.

This mechanism as pictured accounts satisfactorily for the nice adjustment of the mechanical phase of the digestive process to the chemical phase. It requires that food be retained in the stomach until thoroughly mixed with gastric juice, and then regulates its delivery to the small intestine little by little in exact proportion as the food mass becomes impregnated with the digestive juices to which it is next to be subjected, *i. e.*, pancreatic juice and bile. From the teleological point of view the theory of acid control of the sphincter is superior to the theory of mechanical control. It must be admitted, however, that so far as the human pyloric valve is concerned the weight of recent evidence appears to favor the latter theory rather than the former. One must recognize, furthermore, that in the condition of *achylia gastrica*, in which the gastric secretions are deficient in acid, the stomach empties itself successfully. Until further evidence accumulates to clear up the picture one may think of the pyloric valve as reacting to stimuli, perhaps sometimes mechanical and at other times chemical, in such a way that the food is discharged into the intestine gradually, establishing a condition favorable to the successful continuance of the digestive process in the small intestine.

Influence of the Central Nervous System on the Stomach.—The parasympathetic innervation to the stomach is on the whole excitatory, and the sympathetic inhibitory. The statement applies both to gland action and to motility. Stimulation of the vagus nerves causes augmentation of gastric secretion and, on the whole, of stomach movements. In agreement with these findings we note that affective states such as accompany bodily well-being, and which are supposed to find expression through parasympathetic discharges (page 735), are on the whole favorable to digestion. Conversely, affective states which attend threats to security, and which are associated with sympathetic discharges (page 735), are definitely unfavorable to digestion.

ABSORPTION FROM THE STOMACH.

The constituents of an ordinary meal potentially absorbable from the stomach, in the sense that they are soluble, are water, salts, sugar and perhaps vitamins. The digestive processes in mouth and stomach add the special sugar, maltose and the early split products of proteins, which are also soluble. The materials that are absorbable in the sense that they are ready for direct utilization by the tissues are water, salts, any hexose sugars that may have been eaten and again the vitamins.

Direct experiment shows that under the conditions usually prevailing there is no demonstrable absorption of water, either during digestion or between times. Salts are said not to be absorbed except when in concentration of 3 per cent or more, and sugars, either monosaccharides or disaccharides, except when in concentration of 5 per cent or more. At these high concentrations the irritation of the stomach wall becomes so pronounced that vomiting (see below) is nearly always induced. There is little likelihood, therefore, of any significant absorption of either of these classes of materials. Whether there is absorption of vitamins from the stomach is not known.

The most striking example of absorption from the stomach is furnished by alcohol, which is said to be so rapidly and completely absorbed, no matter how heavy the dose, that practically none ever enters the intestine. In the course of its absorption alcohol carries a good deal of water through the stomach wall with it. Alcohol is known to irritate the gastric mucosa markedly. In common with other gastric irritants, *i. e.*, pepper, mustard and similar condiments, it is said to cause absorption of sugar and salts, possibly also of proteoses and peptones, at the low concentrations in which they are ordinarily present.

VOMITING.

Vomiting is a complex highly coördinated reflex act mediated by a "vomiting center" located in the medulla in the sensory nucleus of the vagi (ala cinerea). Afferent impulses resulting from stimulation of the gastro-intestinal tract, other abdominal viscera, the heart or the labyrinth or eyes, as in sea-sickness, are particularly likely to arouse the center to its characteristic discharges. The center itself may be more excitable at one time than another. It is probable that vomiting usually implies hyperexcitability of the center, although certain specific stimuli, such as over-distention of the stomach, tickling the back of the throat, or irritation of the gastric mucosa with an emetic like ipecacuanha, may induce vomiting when the center is entirely normal. The drug, apomorphine, which is particularly inducive of vomiting, is said to act by making the center so excitable that the ordinary streams of afferent impulses through the medulla set the center off.

In the act of vomiting the salivary glands are usually actively stimulated, leading to profuse salivation. The pyloric part of the stomach contracts strongly, the fundus relaxing simultaneously, so that all the stomach contents are forced into the fundus. The cardiac sphincter and esophagus are thought to relax and become flaccid. Contractions of the diaphragm and the *expiratory muscles* of the chest occur coincidently instead of in sequence as in forced

breathing (page 376), forcing the stomach contents into the esophagus. The diaphragm then relaxes and there is a powerful contraction of the abdominal walls by which the abdominal organs are forced upward, thus raising the pressure on the esophagus. This pressure expels the vomitus to the exterior. It is thought that antiperistalsis of the esophagus may aid in this last stage.

The nausea that usually attends vomiting is probably due to antiperistalsis in the small intestine (page 417). Most conditions or stimuli that evoke the vomiting reflex also cause intestinal antiperistalsis, and hence nausea. The relation is not invariable, however. In many persons vomiting can be elicited by mechanical irritation of the back of the throat with little or no discomfort.

Summary.

Digestion consists essentially in the hydrolysis of polysaccharides and disaccharides to glucose; proteins to amino-acids and fats to a form enabling them to be transported across a watery membrane and suspended in watery plasma. The hydrolyses are catalyzed by a series of eight or nine enzymes.

The *digestive process* consists of muscular and glandular activities, controlled in part through the autonomic nervous system, and in part through mechanical, chemical and nervous influences brought to bear locally. These are coördinated in such manner that the food mass is exposed to the various enzymes under conditions favorable to their action.

Mastication is a muscular act under the control of somatic motor nerves. It may be volitional, but is commonly performed as a conditioned reflex. The purpose is to break the food particles into small portions, so as to present large surface for enzyme action, and to secure thorough admixture with saliva.

Saliva is the secretion of the salivary glands. The gland cells are subject to secretory stimulation through the autonomic nervous system. The blood supply to the glands is also subject to regulation through the same. The glands are aroused to action either reflexly, by means of sensory stimulation originating in the buccal cavity, or as the result of out-pouring of impulses over the parasympathetic system in connection with certain affective states. In man affective states leading to sympathetic discharges are inhibitory to salivary secretion.

Saliva has the continuous function of keeping the throat and esophagus moist and of preventing continuous thirst. The digestive function of saliva consists in part of moistening the food and in part of introducing salivary diastase.

Salivary diastase converts starch through a series of dextrins to the disaccharide maltose. It acts at hydrogen-ion concentrations near neutrality.

Deglutition occurs in three stages. The first is the squeezing of a food bolus through the isthmus of the fauces; the second is the shooting of the bolus across the pharynx to the entrance of the esophagus, and if the mass is watery enough down the esophagus to the cardiac sphincter; the third is the passing of a peristaltic wave down the esophagus. Stages 1 and 2 and the first part of stage 3 are performed by skeletal muscles. The part of stage 3 that involves the lower portion of the esophagus is performed by smooth muscle. Stage 1 may be volitional, but is usually reflex. Stages 2 and 3 are strictly reflex. On account of the complexity of the whole act a *deglutition center* is postulated.

The *cardiac sphincter* guards the opening between stomach and esophagus, and prevents the pressure of the stomach walls upon the stomach contents from forcing the latter back into the esophagus. Swallowed food enters the stomach, in spite of the pressure exerted there, through a combination of relaxation of the sphincter with arrival of a peristaltic wave in the esophagus.

The coördination of relaxation of the sphincter with the arrival of a peristaltic wave depends on the operation of the so-called *myenteric reflex*. This consists of an area of relaxation preceding an advancing ring of contraction. It occurs in the lower part of the esophagus and in the small intestine, and is mediated through the long fibers of the myenteric plexus.

Swallowed food is *stratified in the stomach* in such a way that the first to enter is in contact with the walls, and later entries are imbedded and more deeply within the food mass.

As the stomach fills with food its tonus is so adjusted that the *mean pressure* upon the contents remains about uniform.

The *food is churned* by a succession of peristaltic waves arising in the middle third and sweeping in close succession toward the pyloric valve. The waves are complicated in form by concurrent rhythmic tonus changes, whose periods make up the so-called gastric cycles. The food in the main part of the fundus is not involved in the churning. It accordingly remains unmixed with acid gastric juice and salivary digestion continues uninterrupted within it.

The essential constituents of gastric juice are *hydrochloric acid*, the proteolytic enzyme, *pepsin*, and the milk-clotting enzyme, *rennin*. Pepsin appears to be secreted as inactive pepsinogen and activated by HCl. Its action is to catalyze the hydrolysis of proteins to proteoses and peptones. Pepsin is active at hydrogen-ion concentrations of about pH 1.6.

The *gastric glands* secrete continuously at the rate of about 30 ml. per hour on the average. During the eating and digesting of meals the secretion is markedly augmented, rising to as much as 3.5 ml. per minute. The early augmentation is due to the "appetite secre-

tion," aroused as a conditioned reflex when food is eaten with appetite. The subsequent augmentation depends, apparently, on the presence of partly digested proteins, meat extracts or milk in the stomach. How these materials act to stimulate the glands is not certain. The widely accepted theory that they react with a constituent of the pyloric mucosa to form *gastrin*, a hormone which excites the gastric glands, has recently been called seriously in question.

Measurement of peptic action is usually made by means of *Mett's tubes*. The criterion is the length of the column of coagulated egg-white dissolved in a given time.

The *emptying of the stomach* depends on periodic brief relaxations of the pyloric sphincter by which the stomach contents are delivered little by little to the duodenum. The sphincter operates according to the myenteric reflex, relaxing when stimulated from the stomach side and contracting when stimulated from the duodenal. When stimulated concurrently from both sides the sphincter remains contracted. Adequate stimuli may conceivably be either mechanical or chemical (hydrogen-ion concentration). The theory of acid control of the sphincter has positive evidence in its support, and it also harmonizes particularly well with the general fact that the digestive processes are nicely coördinated throughout. Considerable evidence has accumulated, however, which appears not to be reconcilable with it.

So far as the central nervous system influences gastric digestion, the effects exerted through the *parasympathetic* system may be described as *favorable* and those exerted through the *sympathetic* system as *unfavorable*.

There is *no significant absorption from the stomach* (except of alcohol) under ordinary conditions. Salts and sugars may be absorbed when present in high concentrations. Alcohol is absorbed rapidly and completely in all concentrations. Gastric irritants cause absorption of materials in lower concentrations than would otherwise be taken up.

Vomiting is a complicated reflex mediated by a "vomiting center" in the medulla. The reflex is aroused by characteristic stimuli from the gastro-intestinal tract, other abdominal viscera, the heart, or the eyes or labyrinth. Hyperexcitability of the center is a usual contributary factor. The act involves contraction of the pyloric region of the stomach, so that the stomach contents are all forced into the fundic region. Following this the stomach contents are forced into the esophagus by coincident contractions of the diaphragm and expiratory muscles, and from the esophagus expelled to the exterior by strong contractions of the abdominal wall. The nausea that usually attends vomiting is presumably due to antiperistalsis of the small intestine.

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CHAPTER XXV.

THE MECHANISM OF DIGESTION: THE SMALL INTESTINE.

CHYME.

The material that enters the small intestine from the stomach is known as *chyme*. It is typically a mixture of saliva and gastric juice, starch, maltose, any sugars that may have been eaten, proteins, proteoses, peptones, melted fats, possibly some swallowed water, roughage and the various salts, vitamins and flavoring materials present in the food. Under ordinary conditions there is no significant absorption from the stomach (page 405), hence the chyme contains everything swallowed plus the contributions due to salivary and gastric action. Its consistency is that of a very thin paste. Its hydrogen-ion concentration, on account of the presence of the HCl of gastric juice, is near a pH of 1.6.

Secretion of Pancreatic Juice.—The first result of the passage of chyme into the duodenum is the evocation of a copious secretion of pancreatic juice. Pavlov perfected a method for bringing to the surface one of the two pancreatic ducts present in dogs, and so establishing a permanent pancreatic fistula. He found that in his experimental animals (which recovered completely from the operation and with care could be kept in health for a long time), a small out-pouring of pancreatic juice began within a minute or two after the beginning of the meal, but copious secretion did not begin until chyme began to pass from the stomach into the small intestine.

This copious secretion occurs after all extrinsic nerves to the pancreas have been cut. It can be evoked by the simple bringing of acid in contact with the duodenal mucosa. The action of chyme is attributed, therefore, to its acid content. Bayliss and Starling showed (1902) that an acid extract of duodenal mucosa injected into the blood stream causes an abundant out-pouring of pancreatic juice. They accordingly postulate the presence of a hormone precursor (which they designate *prosecretin*) in the intestinal mucosa. By reaction with acid this precursor is presumed to be converted to an active hormone *secretin*. The secretin is conveyed to the pancreas in the blood stream and excites it to activity. These observations and the theory based on them antedate the virtually identical gastrin theory of Edkins (page 401) by about four years. In fact,

the latter's work grew directly out of the prior work of Bayliss and Starling. McClure and associates have shown that in man secretin may be formed in the absence of free acid in the duodenum. They conclude that unidentified products of gastric digestion may react with prosecretin to form secretin.

The theory that the pancreas is normally stimulated by the hormone, secretin, is generally accepted, notwithstanding the discovery that the same wide variety of acid extracts of animal and plant tissues that excite the gastric glands (page 402) excite the pancreas also. There are two main reasons why this discovery, so damaging to the gastrin theory, fails to shake the secretin theory. The first is that the secreting cells of the pancreas have no nervous connection with the duodenum, so far as known, other than through the central nervous system, and hence after the extrinsic nerves have been severed cannot well be excited by stimuli applied to the duodenal mucosa in any other way than through the blood stream. The second is found in the fact, referred to previously (page 140), that the proteolytic enzyme in pancreatic juice secreted during the course of normal digestion is in the inactive form of trypsinogen, as is also the case in juice obtained by injection of artificially prepared secretin into the blood, while juice secreted in response to nervous stimulation contains active trypsin. It follows from this that the normal secretion is aroused chemically, and not through some as yet unrecognized nervous channel.

PANCREATIC JUICE.

Pancreatic juice as normally secreted in man is a water-clear liquid of about the same density as saliva (specific gravity of pancreatic juice, 1.0075). It is definitely alkaline, the titrable alkalinity being about equal to that of $\frac{N}{10}$ Na_2CO_3 (Starling). It contains a little mucin, two active enzymes, *pancreatic diastase* (amylopsin) and *lipase* (a fat-splitting enzyme) and an inactive enzyme commonly called *trypsinogen*. The latter upon entry into the intestinal cavity comes in contact with *enterokinase*, a constituent of the intestinal juice (page 419), and is activated thereby to the powerful proteolytic enzyme, *trypsin*.

Neutralization of Chyme Acid.—The first function of pancreatic juice is to act with the alkaline bile to neutralize the acid present in the chyme that enters the duodenum. According to the theory of acid control of the pyloric valve (page 404), this neutralization must occur in each bolus before another can pass the sphincter. Disregarding this theory, the neutralization is still necessary to enable the pancreatic and intestinal enzymes to function, since their optimum hydrogen-ion concentration is near neutrality, and far removed from the pH valve of the entering chyme.

Action of Pancreatic Diastase.—This enzyme acts like salivary diastase (page 392) to hydrolyze starch to maltose through a series of intermediate dextrins. In animals like dogs, which have no salivary diastase, all the starch taken with the food (in the wild state very little) must be hydrolyzed by pancreatic diastase. In man and in the herbivora the action is purely supplementary to that of salivary diastase. The conditions are favorable, moreover, for very complete action, and direct experimentation shows that no starch fails normally of digestion, unless so enclosed in non-digestible materials that diastase fails to come into contact with it.

Action of Trypsin.—Trypsin hydrolyzes any proteins that may escape the action of pepsin. It also hydrolyzes the proteoses and peptones formed in peptic digestion. The hydrolysis is nearly complete, the large molecules being broken up mostly into their constituent amino-acids (page 181). It is interesting, however, that the linkages which hold certain amino-acids together are not affected by trypsin. There are, therefore, always some polypeptides remaining, even after prolonged tryptic digestion. (These remaining linkages are broken by erepsin, page 419.) The amino-acids most readily set free are tyrosine, leucine, aspartic acid, glutamic acid, tryptophane, lysine, argenine and histidine.

Under ordinary conditions the trypsin is either destroyed or loses its effectiveness by the time the lower end of the small intestine is reached. This is important in relieving the posterior portions of the gut from the danger of undergoing digestion through the agency of this powerful enzyme.

Action of Lipase.—Through the action of pancreatic lipase the neutral fats eaten, which in the case of man are mixtures of triglycerides of palmitic, stearic and oleic acids in different proportions, are hydrolyzed more or less completely into their constituent fatty acids and glycerol. The glycerol is soluble in water. The fatty acids promptly combine with the alkali present, contributed largely by the bile (see next paragraph), to form water-soluble soaps. There is no doubt that enough lipase and enough alkali are normally present to saponify all the digestible fat that enters the small intestine. From time to time the question has been raised whether all actually does undergo saponification, or whether part is saponified and the remainder absorbed as fat in emulsified form. The presence in and about the intestinal epithelium of great numbers of leukocytes loaded with fat (page 259) suggests that some, at least, of the fat may be transported from the intestine to the lymph without previous saponification. A fact seeming to prove that all fats are hydrolyzed before being absorbed is that non-hydrolyzable fat-like materials (such as mineral oils) are not absorbed even though they may be present in the intestine in a form that lends itself to emulsification. Bloor emphasizes this fact, pointing out

that by restricting absorption of fats to such as have been hydrolyzed the body guards against the uptake of useless or possibly injurious fat-like substances.

ACTION OF BILE.

Bile is in part an excretory liquid, serving as the channel of elimination of pigments and of cholesterol (Chapter XIV), and in part a digestive liquid. In the latter capacity it contributes definitely to the digestion and absorption of fats. It has been thought by some to play a role also in the digestion and absorption of the other nutrients, but if it does the nature of its action is yet to be learned. The significant constituents of bile as a digestive liquid are: (1) Its alkali (Na_2CO_3 and $NaHCO_3$), which acts with the alkali of the pancreatic and intestinal juices to saponify the fatty acids; (2) its bile salts, sodium salts of taurocholic and glycocholic acids.

The bile acids are compounds of cholic acid, which is a non-nitrogenous compound synthesized exclusively by the hepatic epithelium, with either *taurin*, a derivative of the amino-acid, cysteine, or *glycine* (amino-acetic acid), one of the few amino-acids the body is able to synthesize (page 62). In the presence of bile salts the lipase of pancreatic juice is three or more times as effective in hydrolyzing fats as in their absence. The bile salts also promote the absorption of the soaps which result from lipase action. They are also said to promote intestinal peristalsis (page 416). When bile is absent from the intestine, as through occlusion of the bile duct, the entire digestive process is disturbed. An obvious factor in the disturbance is the failure of the fats to be fully digested and absorbed. They accordingly tend to remain in the gut, and by their mere presence, in smearing themselves over the watery constituents of the intestinal contents, act to prevent the latter in turn from being digested and absorbed properly. Whipple considers bile to be of even more deep-seated significance than this. He states that "secretion of bile into the intestine is necessary for normal health and even for actual continuation of life beyond a few months' period."

Secretion of Bile.—Bile is apparently formed continuously at the average rate of 500 to 1000 ml. per day. As formed by the liver cells it is 97 to 98 per cent water and 2 to 3 per cent solid constituents. About one-half the solid portion consists of bile salts. The balance is a mixture of inorganic salts (mostly carbonates), with excretory substances and traces of lipoids. Various factors, of which the diet is perhaps chief, determine the rate and volume of secretion. The out-pouring into the intestine does not necessarily or usually coincide with the formation by the liver. This is because

the gall-bladder (or in animals like the horse, with no gall-bladder, the wide hepatic duct) acts as a temporary reservoir in which part of the bile may be accommodated and from which it may be ejected intermittently. The gall-bladder has, moreover, a remarkable power of concentrating the bile that enters it. This is done mainly by absorbing out most of the water, although some mucin and perhaps some cholesterol are said to be added to the bile by the cells of the gall-bladder. In the dog the gall-bladder is able to reduce bile to one-fifth to one-tenth its original volume in twenty-four hours (Rous and McMaster).

The view has been held that when no intestinal digestion is going on little or no bile enters the gut, most or all of it being then diverted into the gall-bladder. During intestinal digestion, on the other hand, the same secretin that causes pancreatic juice to be poured out is said to cause the gall-bladder to contract and eject its contents more or less gradually, and at the same time to excite the liver cells to a more active secretion, so that the resultant abundant out-pouring is composed mainly of gall-bladder bile in the early part of intestinal digestion and of newly formed bile in the later stages (Boyden).

Recent evidence seems to show that there is more of a flow of bile into the gut when no digestion is in progress than was formerly believed, and that the augmentation during digestion may be due to various factors, nervous, chemical and vascular (augmented blood supply) and not solely to secretin action.

Bile is secreted under a low pressure. When obstruction occurs the pressure rises to about 240 to 270 mm. bile, in human patients, whereafter the bile filters from the minute bile passages to the blood capillaries, establishing the condition known as *obstructive jaundice*. The resistance to filtration of bile offered by the intervening membranes is obviously so slight that only this small rise of pressure is necessary to overcome it. So far as can be determined, obstruction causes no diminution in bile formation. The bile is discharged through the blood and urine instead of through its normal outlet.

The Circulation of Bile Salts.—A remarkable fact about the bile salts is that they are rapidly and completely reabsorbed into the blood by the intestinal mucosa in the regions beyond the duodenum. This blood, being in the portal circulation, carries them directly back to the liver, where they are taken up again by the liver cells to reappear in the bile. There is thus a definite *circulation of bile salts*. The obvious corrallary to this circulation is that there can be no new formation of bile salts except to make good such accidental or incidental losses as may occur. Otherwise bile salts would accumulate continuously and indefinitely. In striking contrast to this normal situation is that presented when there is a biliary fistula, permitting escape of the bile to the exterior as fast

as secreted. In human beings in this state 500 ml. or more of bile may be poured out daily, all containing the normal concentration of bile salts. This implies a formation per day of 7 to 15 gm. of the latter. There is evidently a mechanism that acts to maintain the normal percentage of bile salts. If they come to the liver in sufficient quantity by reabsorption from the intestine none will be synthesized *de novo*. To the extent to which they fail to be supplied from that source they are synthesized. There must be some loss, by one means or another, for the concentration in the bile of any individual varies from time to time, and differences in diet are known to cause differences in rate of bile-salt formation. Where or how this loss occurs is not known.

MOVEMENTS OF THE SMALL INTESTINE.

Propulsion.—The forcing of successive boluses through the pyloric valve fills the upper end of the duodenum for a length of 10 to 30 cm. The further passage of chyme along the small intestine is due to peristaltic waves which follow the law of the myenteric reflex (page 394). That is to say, an advancing ring of constriction sweeps along, preceded by an area of relaxation. The combination obviously favors the onward movement of the intestinal contents. In Cannon's terminology these are waves of diastalsis (page 397).

The first wave to pass following the entry of chyme into the duodenum dislodges a column 10 cm. or so long and propels it quite rapidly a distance about equal to its length, in other words, into a fresh section of intestine, and hence into contact with a fresh intestinal surface. Having accomplished this the wave dies out, leaving the mass of chyme stationary.

Following the first wave others occur at irregular intervals, each pushing the column of chyme forward about its own length and then ceasing. Meanwhile other columns are entering the duodenum from the stomach, to be pushed forward intermittently in turn by short-running waves. The first column is said (Hurst) to arrive at the ileocolic valve in man in about four to five hours after entering the duodenum. By this time the stomach has usually discharged the major part of its contents (page 403), so that the small intestine contains most of the chyme, disposed in successive short columns, which in many places are in contact with one another, and in others are separated by short intervals. On account of the continuous absorption of nutritive material (page 420) the chyme becomes decidedly attenuated by the time the ileocolic valve is reached.

Under certain conditions peristaltic waves may sweep rapidly over considerable lengths of intestine. The phenomenon is known as *peristaltic rush*. It obviously tends to move the food through

and beyond the small intestine more quickly than usual. It is also possible for peristalsis to occur in the reverse direction (anastalsis, according to Cannon's terminology). This antiperistalsis is not preceded by a wave of relaxation. Its effect is to cause the intestinal contents to move back toward, and usually into, the stomach. In mild attacks of vomiting it is not uncommon for bile to be found in the vomitus. In severe attacks fecal material from the large intestine has been known to be vomited, showing that the antiperistalsis has extended the entire length of the gut. The view that sensations of nausea are due to antiperistalsis in the small intestine is mentioned in another place (page 407).

The Theory of Tonus Gradients.—A fact of importance about smooth muscle is that it may display so-called "spontaneous" contractions (really due to excitation from the accompanying plexus), but does so only in regions of high tonus. Alvarez has developed a theory of intestinal movement, based on this dependence of contraction on tonus. According to this view peristaltic waves originate at points of high tonus and move toward points of lower tonus. It pictures the normal state of the gut to be one in which the maximum tonus is at the forward end, shading off to lower and lower tonus levels, and reaching a minimum for the small intestine at the ileocolic valve. Local irritations of various kinds tend to raise the tonus at particular levels. The short diastaltic movements (previous page) by which the chyme is moved intermittently along the gut might be due, according to this view, to local irritation exerted by the chyme itself. A more pronounced irritation might act to bring on peristaltic rush. An irritation at the lower end of the bowel might either delay the onward movement of chyme by raising the tone there and so abolishing the tonus gradient or might even start waves of antiperistalsis. The main facts of intestinal motility are well explained on this theory. That the small intestine shows definite polarity was demonstrated first by Mall, who resected a segment of intestine, reversed it and sutured it into place again. Although some animals thus treated made a good surgical recovery, they all developed complete intestinal obstruction, and necropsy showed that no chyme was able to pass the reversed section of gut.

Churning.—If a stationary column of chyme in the small intestine is watched by the roentgen-ray method it is usually seen to undergo a series of rhythmic breakings-up and reunitings, as indicated in Fig. 47. The phenomenon is known as "rhythmic segmentation" (Cannon). What happens is that rings of circular muscle contract at space intervals of 2 or 3 cm., breaking the chyme up into corresponding segments. These rings then relax and a new series, spaced midway between the former ones, contract, forming new segments as shown in 3 of the diagram. The process is repeated

rhythmically, often for one-half hour or so, when the movements die out, to be followed presently by a peristaltic wave that propels the food to a fresh section, where the segmentation movements are resumed. It is stated that the segmenting movements are really due to slight waves of contraction passing in rapid succession over the intestine and becoming accentuated, probably by the mechanical stimulus of the underlying food mass, at the regularly spaced intervals at which segmentation occurs.

The rhythm of these movements is most rapid in the duodenum (17 to 21 per minute, according to Alvarez) and decreases toward the ileum, where rhythms of 10 to 12 per minute are seen. Alvarez attributes this difference to the difference in general tonus level, referred to above.

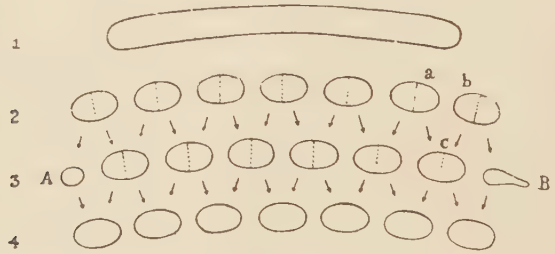

FIG. 47.—Diagram illustrating rhythmic segmentation. (Cannon.) (Starling's Physiology.)

Control of the Central Nervous System over Intestinal Movements.—Both peristalsis and segmentation can proceed normally in an intestine from which all extrinsic nerve connections have been cut away. The central nervous system may, however, influence intestinal action, and in general in the same sense in which stomach action is influenced (page 405). That is to say, parasympathetic discharges (arriving by way of the vagi) are excitatory; sympathetic discharges (over the splanchnics) are inhibitory. The inhibitory action involves both circular and longitudinal muscle coats. The action on the latter coat is used as an exceedingly delicate test for adrenin (page 201). It is found that strips of longitudinal intestinal muscle beating "spontaneously" are inhibited by adrenin in dilution of 1 to 400,000,000 or more.

INTESTINAL JUICE.

The glands in the intestinal mucosa (the crypts of Lieberkühn) secrete the last of the digestive juices, known as intestinal juice or *succus entericus*. There is a more or less continuous secretion of liquid into the intestine, as can be proved by separating out a short

section of gut and connecting it with the exterior by suturing one or both ends into abdominal fistulæ (establishing the so-called Thiry-Vella fistula). The continuity of the main intestine is restored meanwhile by an end-to-end anastomosis.

When no digestion is going on intestinal juice is secreted slowly, both into the isolated pouch and into the main intestine. There is a perceptible augmentation shortly after beginning a meal (perhaps due to the improved blood supply that attends activity of the alimentary tract). Coinciding with the out-pouring of pancreatic juice is a copious flow of intestinal juice. There is little reason to doubt that this flow is initiated by secretin in a manner corresponding to that already described for pancreatic juice (page 411).

The total average secretion of intestinal juice is estimated at 3 liters a day in man. Its rather large volume restores to the lower part of the gut about as much water as is absorbed out from the upper part, thus insuring that the chyme shall be kept sufficiently liquid throughout the whole length of the small intestine.

Intestinal Enzymes.—The digestive action of intestinal juice consists in the final breaking of such amino-acid linkages as are impervious to trypsin action (page 413), and thus carrying protein digestion to completion, and the conversion to hexose sugars of the disaccharides (maltose from starch digestion, sucrose eaten as such and lactose taken in milk).

These final hydrolyses are catalyzed by enzymes that are either secreted into the intestinal juice or retained in the cells of the intestinal mucosa. The intestinal juice obtained from a Thiry-Vella fistula has a markedly less potent digestive action than does an extract of intestinal epithelium, a fact which suggests that the enzymes function chiefly during the absorption of the polypeptides and disaccharides through the intestinal wall, rather than within the lumen of the gut.

The enzymes are *erepsin*, a proteolytic enzyme, which does not act on large protein molecules, but hydrolyzes peptones and simpler polypeptides very completely to their ultimate amino-acids; and three inverting enzymes, *maltase*, *sucrase* and *lactase*, by which the corresponding disaccharides are converted to hexose sugars. An additional constituent, *enterokinase*, which activates trypsinogen (page 140), has been thought to be an enzyme, but recent work calls this in question.

BACTERIAL ACTION IN THE SMALL INTESTINE.

The mammalian small intestine harbors normally a rich bacterial flora. The organisms live on the intestinal contents. In the upper part of the gut, on an ordinary mixed diet, sugar is always present in relatively high concentration, and the bacterial action is pre-

dominantly fermentative, lactic acid being the chief product. The hydrogen-ion concentration accordingly tends to shift in the acid direction. In the lower part of the small intestine, where the sugar has usually been pretty completely absorbed out, the organisms may be forced to a metabolism based on proteins. The action then becomes putrefactive (page 426), and the hydrogen-ion concentration shifts in the alkaline direction.

The only definite service intestinal bacteria are known to perform is that of digesting raw cellulose. This polysaccharide is an important constituent of the diet in most herbivora. No enzyme that will hydrolyze it is secreted by the digestive glands. It is, however, more or less completely hydrolyzed by bacterial action. (In forms, like the rabbit, with a large cecum, this action is an important feature of the digestive process.) Raw fruits and vegetables are not eaten by man primarily for their cellulose content, but for such starch or sugar as they contain, and, as we now realize, for their vitamins (page 193). It is probably true that to some extent, particularly in the case of lettuce, the digestive action of the bacteria on the cellulose cell walls sets free vitamins that would otherwise not be accessible for absorption.

In the small intestine the non-pathogenic bacteria may do disservice by causing excessive fermentation, with production of large volumes of CO_2 to cause distress, or of large quantities of organic acids to irritate the intestinal lining and produce diarrhea. If the diet is deficient in carbohydrate or excessive in protein, or if there is a stasis of the ileum (page 427), the organisms may cause enough putrefaction to do harm (page 426).

ABSORPTION FROM THE SMALL INTESTINE.

On account of the presence of the villi the surface of the intestinal epithelium is enormously enlarged over what it would be otherwise. The segmenting movements (page 417) bring the intestinal contents into particularly intimate contact with the whole epithelial surface. Movements of the villi themselves are described presumably helping to establish this contact. Conditions favorable for absorption are thus maintained. The actual mechanism of the absorptive process is not understood. Simple dialysis may account for it to some extent, but by no means completely. It is found, for example, that if some of an animal's own serum is placed within its intestine the serum will be completely absorbed into the blood in course of time. Furthermore, differential absorption, *i. e.*, the selection of some substances and the rejection of others of equal or less size of molecules is a characteristic property of intestinal epithelium. Some evidence indicates solubility in the constituents of the cell membranes (especially the phosphatides) to be an important factor in

the differential action, soluble substances being absorbable, insoluble substances not. Other evidence shows active metabolism on the part of the epithelial cells of the intestinal villi to be concerned in the process, with the result that materials are caused to be taken up more or less independently of the osmotic or diffusion gradients present. Injury to the intestinal epithelium, as by treatment with sodium fluoride, cuts down its absorptive power materially, and is said to reduce absorption to the status of simple osmosis and dialysis.

Hexoses and amino-acids pass directly from the intestinal epithelium into the capillaries. Their subsequent fate is described elsewhere (pages 176 and 181). Fats, which presumably enter the epithelial cells as mixtures of soap and glycerol (page 413), are resynthesized into fat during their passage through the epithelium. Repeated investigation has shown that no fats are present as such in the borders of the cells facing on the intestinal lumen. Deeper within the cells fat droplets are to be seen (Fig. 48). The mechanism by which the fat is expelled from the inner faces of the epithelial

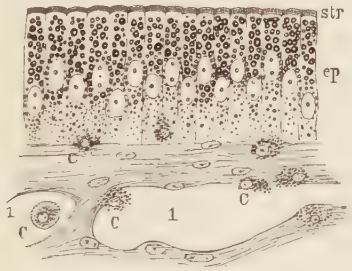

FIG. 48.—Intestinal epithelium (frog) during fat absorption. The cells, *ep*, are seen loaded with fat except at their intestinal borders. Leukocytes loaded with fat are shown at *c; l*, lacteal. (From Schäfer's Essentials of Histology, by permission of the author.)

cells is not certain. Schaefer is the chief proponent of the view that leukocytes play an important role (page 259). Whatever the mechanism, a feature of interest is that upon leaving the epithelium the fat becomes broken up into particles of ultra-microscopic fineness, described as "fat dust."

About 60 per cent of the total quantity of fat absorbed is known to pass into the lymphatics of the intestine. The milky lymph, known as *chyle*, makes a striking picture in the lacteals of an animal killed in the midst of active fat absorption. Indeed, it was the marked resemblance of the chyle to milk that led Aselli to bestow the name lacteals upon these vessels in 1622. The lacteals drain into the *receptaculum chyli*, whence the thoracic duct conveys the chyle to the blood. How the remaining 40 per cent of fat reaches the blood is not known. Tests of portal blood have failed to reveal

an increase in the proportion of fat in the blood draining the intestine during fat absorption. The tests thus far available are not so delicate, however, as is to be desired, and it is quite probable, in fact presumable, that most of the fat that does not pass by way of the thoracic duct enters the blood directly, but too gradually to be detected by present methods. The further fate of the fat is considered in another place (page 185).

Accordingly to the studies of London, absorption goes on actively throughout the small intestine. The carbohydrates appear to pass through the final steps in digestion and to be absorbed somewhat more rapidly than the proteins, so that at the lower end of the gut the latter tend to be in higher concentration than the former (page 420). This relationship depends, of course, to a large extent on the diet. It is probable that under ordinary circumstances virtually all absorbable sugars and fats and most of the amino-acids are absorbed by the time the chyme reached the ileocolic valve. The total volume of chyme is markedly less at the valve than in the duodenum, and the percentage of water is considerably higher. There is considerable absorption of water, especially in the upper part of the gut, but a resecretion of about as much in the form of intestinal juice (page 419) in the lower segments. The net result is to maintain the water content at about a uniform level the whole length of the small intestine.

Summary.

The *chyme* that enters the small intestine is ordinarily a mixture of everything swallowed plus the contributions due to salivary and gastric action. It has the consistency of a thin paste and a pH value near 1.6.

The first effect of the entry of chyme is the formation of *secretin* by a reaction between constituents of the chyme and prosecretin present in the intestinal mucosa. Secretin is a hormone which excites the pancreas to pour out pancreatic juice.

Pancreatic juice as normally secreted contains *pancreatic diastase*, fat-splitting *lipase* and *trypsinogen*. The latter is a weak enzyme which is activated by contact with intestinal *enterokinase* to form the proteolytic enzyme *trypsin*. These enzymes are active in nearly neutral media. The acid of the chyme must, therefore, be neutralized by the alkaline pancreatic juice and bile before the enzymes can function.

Pancreatic diastase supplements the action of salivary diastase, splitting to maltose any starches that may escape salivary action.

Trypsin hydrolyzes proteins, including proteoses and peptones, to amino-acids. The hydrolysis is nearly complete, but not quite. Some amino-acid linkages are not affected by trypsin.

Pancreatic *lipase* splits neutral fats to fatty acids and glycerol. The glycerol is soluble in water; the fatty acids react with alkali contributed by the pancreatic juice and bile to form water-soluble soaps. The present view is that no fats are absorbed except such as undergo complete saponification.

Beside contributing alkali *bile* aids fat digestion through its content of bile salts. These increase the effectiveness of lipase threefold or more. They also improve the absorption of soaps, and promote intestinal peristalsis.

Bile is formed continuously by the liver but secreted intermittently into the intestine. During periods of lessened secretion the surplus is diverted into the gall-bladder, where it undergoes marked concentration. When the flow to the intestine is obstructed bile filters at low pressure from the bile capillaries into the blood capillaries, giving rise to obstructive jaundice.

The *bile salts* that enter the duodenum in secreted bile are absorbed into the portal blood in the jejunum and ileum and taken up from the blood by the liver cells to reappear in the bile. There is thus a "circulation of bile salts," and no synthesis of new bile salts except to make good such losses as occur, or in connection with a temporary increase in the rate of bile formation.

Chyme is *propelled through the small intestine* by successive irregular waves of diastalsis, *i. e.*, advancing rings of contraction preceded by areas of relaxation. The waves are usually short-running, just sufficing to move small chyme masses forward into fresh regions of gut. Occasionally waves sweep rapidly for considerable distances (peristaltic rush). Antiperistalsis may also occur under certain conditions.

Alternating with waves of propulsion are movements of *rhythmic segmentation*, whose effect is to churn the chyme and bring it into intimate contact with the intestinal epithelium.

The *parasympathetic* autonomic system is in general *excitatory* and the *sympathetic* system *inhibitory* to the small intestine.

There is a more or less continuous secretion of *intestinal juice*, markedly augmented during periods of digestion, presumably through the action of secretin. The volume is sufficient to keep the chyme liquid throughout the length of the small intestine. The intestinal enzymes are: *Erepsin*, which breaks such amino-acid linkages as are unaffected by trypsin; and three inverting enzymes, *maltase, sucrase* and *lactase*, by which the corresponding disaccharides are converted to hexose sugars.

Bacterial metabolism in the small intestine is fermentative in the upper portions, where sugar is present in abundance, and usually putrefactive in the lower portions, where proteins are the only nutrients available. A certain amount of service to the human organism is done by intestinal bacteria in digesting raw cellulose. Disservice may ensue from excessive fermentation or putrefaction.

The intestinal epithelium has the property of *selective absorption* highly developed. A definite absorptive action is implied, based on the metabolism of the epithelial cells and largely independent of osmotic and diffusion gradients. Hexoses and amino-acids pass directly from the intestinal epithelium into the blood. Fats are resynthesized within the epithelial cells and passed, in the form of ultramicroscopic "fat dust," mainly to the lacteals and thence by the thoracic duct to the blood stream. The portion that does not enter the lymphatic channels is presumed to pass directly into the intestinal capillaries.

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CHAPTER XXVI.

THE MECHANISM OF DIGESTION: THE LARGE INTESTINE.

THE PROXIMAL COLON.

Movements of the Proximal Colon.—Masses of watery chyme are propelled at intervals through the ileocolic valve into the proximal colon. In man the large intestine is sacculated, and its movements are difficult to follow in detail by the roentgen-ray method. The description of colonic behavior given by Cannon for the cat appears however, to hold in the main for man, and is presented here on that understanding. The ascending colon is quiet and relaxed at the instant of entry of chyme, but immediately thereafter goes into a state of strong contraction by which the contents are pressed toward the transverse colon. The contraction subsides shortly and is succeeded immediately by rhythmic waves of antiperistalsis; these arise from tonus rings that form in the transverse colon; they pass backward toward the ileocolic valve. The waves continue for two or three minutes, at the end of which time the proximal colon and cecum are again normally full. The waves are waves of anastalsis, *i. e.*, antiperistaltic waves not preceded by areas of relaxation (page 417). By their action the onward movement of the contents of the ascending colon is delayed, favoring the absorption out of water. If the anastaltic movements become unduly active they may force material back through the ileocolic valve into the small intestine (page 417). These movements alternate with periods of quiescence during which more chyme enters from the small intestine, forcing the chyme already in the proximal colon along toward the transverse portion of the gut. The average time required for the passage of material through the ascending colon is given as about two hours (Hertz).

Absorption of Water from the Proximal Colon.—During the stay of chyme in the ascending colon water is being absorbed out, making the consistency more and more pasty. The material passing on into the transverse colon is forced there mainly by the entry of more chyme into the proximal colon from the ileum; this action is supplemented, however, by the occasional strong contractions of the ascending colon described above. The absorption of water is so active that the material entering the transverse colon has already begun to take on the consistency of feces.

Bacterial Action in the Colon.—The proximal colon harbors a rich bacterial flora, similar in the main to that of the small intestine (page 419). The bacteria are so abundant (33×10^{12} excreted daily by normal adults; MacNeal, Latzer and Kerr) that their bodies contribute 46 per cent of the total nitrogen of the feces. The bacterial metabolism is like that of the ileum, *i. e.*, based on unabsorbed protein residues and hence predominantly putrefactive. Among the products of putrefaction phenol, indol, skatol and ammonia are noteworthy. The first three are absorbed regularly from the intestine into the blood, combine with sulphuric acid to form *conjugated sulphates* (indol and skatol are first oxidized to indoxyl and skatoxyl), and are eliminated from the kidneys in the urine (page 234). The ammonia is converted in the liver to urea (page 182), and in the latter form is also eliminated in the urine. Histamin, a capillary dilator, and tyramin, a capillary constrictor, are both said to be formed in the intestine as putrefaction products. Hydrogen sulphide is another usual product.

AUTOINTOXICATION.

The age-old view that the body is poisoned by absorbed products of intestinal putrefaction was made by Metchnikoff the basis for a conception according to which many of the ills to which flesh is heir, including that most dreaded of all, old age, are due to autointoxication. The validity of the Metchnikoff conception has, however, of late years been seriously called in question. There is no doubt that putrefaction products are absorbed from the intestine, but there appears to be no convincing evidence that these products are harmful in the amounts in which they are ordinarily absorbed, although if the absorption is for any reason excessive they may be injurious. There is evidence that babies and young children suffer ills traceable directly to bacteria in the gut, but many investigators hold that these ills are due to the entry of the bacteria themselves into the blood and tissue spaces, and not to the absorption of products of putrefaction. They represent infection (latent or subinfection usually) rather than intoxication. The untoward symptoms, commonly ascribed to autointoxication, that usually develop as the result of constipation are probably to be explained as the mechanical effect of fecal impaction. Thus while autointoxication undoubtedly exists, it is apparently much less common than is generally believed, and probably implies a more deep-seated gastrointestinal disturbance than the mere stasis of constipation.

FOOD POISONING.

While it appears that the danger of poisoning by products of intestinal putrefaction probably has been overstressed, there is no

doubt that poisons introduced with the food can and do cause serious harm. Contamination of rye flour with an ergot-containing fungus has caused repeated epidemics of ergot poisoning in rye-using countries. Poisoning with the toxin of Claustridium botulinum (botulism) in improperly canned meat or vegetables is responsible year by year for a number of deaths in various parts of the world. Although most of the attacks commonly ascribed to "ptomain poisoning" are now believed to be due to acute infection rather than intoxication, there nevertheless occur acute ptomain-like poisonings that appear to be true intoxications. There are likewise the well-known individual susceptibilities, which cause some people to suffer from eating shell fish, others from fresh strawberries or apricots, still others from veal or eggs, and so on.

ABSORPTION FROM THE DISTAL COLON.

The contents of the transverse colon are typically fecal (page 425). They consist of undigested residues of the food, chiefly cellulose and the tougher connecting tissue portions of meat, together with small quantities of bile pigments (page 432), masses of bacteria and varying quantities of the products of intestinal putrefaction. It is noteworthy that most of the material subject to putrefaction has been acted upon by the time the material enters the transverse colon, and most of the bacteria in the region are consequently dead, having been starved out. In comparison with the active absorption from the ascending colon there is relatively little absorption, either of water or of putrefactive products in the distal colon. The fecal material is not watery enough to be effectively churned by the colonic movements, hence only that which happens to come to the surface of the fecal mass is exposed to the absorptive action of the colonic mucosa. This slightness, both of bacterial action and of absorption, is important in connection with the question of autointoxication, for roentgen-ray studies show that under ordinary conditions material passes the whole length of the gut from stomach to transverse colon about as quickly (six to eight hours) in persons suffering from constipation as in non-constipated individuals, the delay in evacuation being usually confined wholly to the distal colon. The view that the prolonged retention of feces promotes autointoxication by allowing longer time, both for the formation and the absorption of putrefactive products, is thus seen to be subject to over-emphasis. In contrast, it should be noted that intestinal stasis high enough to involve the ileum is typically followed by true intoxication. The contents of the ileum are so watery that putrefaction and absorption can both go on without hindrance in chyme that is prevented unduly from passing on to the proximal colon where the water is rapidly absorbed out.

MOVEMENT OF FECES THROUGH THE DISTAL COLON.

Observations in man by the roentgen-ray method indicate that the contents of the distal colon are moved toward the rectum by strong peristaltic waves occurring at longer or shorter intervals and lasting for only a few seconds. There are probably marked individual variations in the frequency of these waves. In many persons they appear to occur only when food is taken, suggesting that the stimulus to colonic peristalsis may arise from the stomach (the so-called gastro-colic reflex). It is probable that the bulk of indigestible material (roughage) in the gut has something to do with the frequency as well as the effectiveness of the waves, bulky feces being propelled more rapidly than feces of small volume. According to the tonus gradient theory of Alvarez (page 417), the essential condition for the occurrence of these waves is the existence of higher tonus in the transverse colon than in the sigmoid flexure and rectum. Any condition that makes the tonus in the latter region unduly high (the irritation from hemorrhoids, for example) lowers or even reverses the gradient, and so is highly likely to hamper the normal movement of feces through the bowel.

An interesting fact about the passage of material through the distal colon is that the feces do not ordinarily form a continuous column. When one of the occasional peristaltic waves passes the junction between the transverse and descending colons (the splenic flexure) it sweeps a mass of feces all the way to the sigmoid flexure. If this mass has not been passed on into the rectum by the time another arrives the latter piles up on the one that preceded it. Thus the lower end of the pelvic colon fills before the upper.

The onward movement of material from the sigmoid flexure into the rectum is due to peristaltic waves that are usually less frequent than those that sweep over the transverse colon. In individuals of regular habits the passage of material into the rectum may occur just once daily, and at practically the same hour, for weeks or months together.

Defecation.—Defecation is an act, partly volitional and partly automatic, evoked solely, so far as known, by stimuli arising from distention of the rectum. Normally this distention is due to the entry of fecal material into the rectum from the pelvic colon. However, an equally imperious impulse to defecation follows distention of the rectum *per anum*. In order for defecation to occur the external and internal anal sphincters must relax, and pressure must be brought to bear on the rectal contents.

The relaxation of the external anal sphincter is practically always in adults an act of definite volition. This sphincter is composed of skeletal muscle, and is normally in a state of fairly strong continuous tone. The tone is maintained, in the manner characteristic

of skeletal muscle, by constant discharges through somatic motor neurons (page 692). When the motor neurons are cut the tone disappears. The sphincter differs, however, from other skeletal muscle structures in that the tone which disappears when the motor nerves are cut is reëstablished in a short time through the operation of some unknown intrinsic mechanism (Goetz). The sphincter can be excited volitionally to a more intense contraction than that maintained by its normal tone. It can also be relaxed volitionally, an act, as stated above, essential to and the first step in normal evacuation.

The internal anal sphincter is a smooth muscle structure. It receives the double autonomic innervation characteristic of the viscera (page 129). Whether the relaxation of the sphincter in normal defecation is brought about through one or the other of its extrinsic nerves, or whether through the action of an intrinsic mechanism is not known, although it is known that in experimental animals evacuation can occur after section of all extrinsic nerves.

The second factor in evacuation, namely the bringing of pressure to bear on the rectal contents, may be achieved in either of two ways or by the two in combination. One of these is the volitional raising of intra-abdominal pressure. The rise of pressure is brought about by coincident contractions of the diaphragm and the abdominal and thoracic expiratory muscles (page 366), the glottis being closed meanwhile. The effect of this pressure rise is primarily to crowd additional fecal material from the sigmoid flexure on into the rectum, thus distending it more than before. The abrupt distention of the rectum arouses peristaltic waves, both in its walls and in the walls of the pelvic colon, by which the contents are propelled toward and through the relaxed anal canal. If the feces are not too dry the peristaltic waves can accomplish evacuation without any further aid from the expiratory muscles. Frequently, however, it is necessary to supplement the rectal and colonic peristalsis by vigorous or even severe expiratory efforts with closed glottis. A complete evacuation clears both the rectum and the sigmoid flexure of their fecal contents.

Constipation.—The rectum is not a simple straight tube, but is subdivided, usually into three regions, by the so-called "valves of the rectum." Furthermore, the anal canal, which has only a fraction of the diameter of the rectum itself, makes nearly a right angle with the rectal axis. It follows that the feces are expelled readily only when sufficiently moist to be plastic. This degree of moisture implies a stay of not too long duration in the intestine, for while absorption of water is less active in the distal colon and rectum than in the proximal colon, it nevertheless goes on continuously, so that if feces are too long retained the dry and hard consistency characteristic of constipation is taken on.

Various conditions may lead to the overlong retention of feces. The normal impulse to evacuation may be disregarded or purposely restrained; on account of the presence of hemorrhoids or some other irritation, the peristaltic waves essential to evacuation may develop only feebly or not at all; it may be that the bulk of fecal material is too small to distend the rectum sufficiently to evoke active peristalsis. In any event the rectum usually adjusts its tension shortly in the manner typical of smooth muscle structures (page 93), so that the stimulus due to distention subsides. It is then possible for fecal material to remain in the rectum without arousing further impulses to evacuation until it is so dry and hard that defecation becomes difficult. Meanwhile fecal material continues to accumulate in the distal colon and to be passed from time to time into the rectum. Thus if the situation is not relieved both the rectum and the distal colon gradually become charged with feces which continually become drier and harder (the condition is known as fecal impaction).

Very definite symptoms develop in many persons, although not in all, as the result of over-long retention of feces. The symptoms include mental haziness, "dopiness," malaise, headache, coated tongue, poor appetite and so-called "biliousness" (quoted from Alvarez). These are the acute symptoms generally attributed to autointoxication. In the opinion of Alvarez they are really due to nervous and mechanical disturbances (reversal of tonus gradients) arising from fecal impaction in the lower bowel. Much evidence is adduced in support of this view. Particularly cogent is the well-known fact that the symptoms are usually much ameliorated, and frequently disappear completely, immediately following evacuation. It is obvious that symptoms due to intoxicants absorbed from the bowel and circulating in the blood would scarcely subside so promptly. Fully as significant is the observation that simply packing the rectum with cotton produces all the symptoms listed above.

The suggested explanation is that the distention of the lower bowel reverses the normal tonus gradients of the alimentary tract (page 417), and also stimulates receptors present in the walls of that part of the gut. These two effects in combination are looked upon as responsible for the symptoms, although how they act is not yet satisfactorily explained.

Summary.

The *movements of the proximal colon* consist of occasional strong contractions, immediately subsequent to the entry of chyme from the ileum, succeeded by waves of antiperistalsis. The effect of the latter is to delay the onward movement of chyme into the distal colon.

There is *active absorption of water* from the chyme in the proximal colon. The result is that the material entering the transverse colon has already begun to take on the consistency of feces.

Bacteria are very abundant in the proximal colon; their metabolism is predominantly putrefactive. Characteristic products of putrefaction are absorbed into the blood and eliminated in the urine.

Autointoxication (poisoning by the absorbed products of intestinal putrefaction) appears to be less common than has been generally supposed. The frequent symptoms usually attributed to it are probably due, in the majority of cases, to infection by absorbed living bacteria in infants and to the mechanical effects of fecal impaction in adults.

Harmful substances taken inadvertently with the food are absorbed from the intestinal tract, as is evidenced by the occurrence of various types of *food poisoning.*

There is relatively little either of bacterial action or of absorption in the *distal colon.* Retention of material in that region is not, therefore, particularly inducive of autointoxication.

Propulsion of contents through the distal colon toward the *rectum* appears to be by means of occasional short-lasting peristaltic waves. As these waves pass the splenic flexure they sweep the contents in their grip all the way to the sigmoid flexure. The lower end of the pelvic colon, therefore, fills before the upper.

Defecation is partly volitional and partly automatic. The volitional factors are relaxation of the external anal sphincter and the raising of intra-abdominal pressure by coincident contractions of the diaphragm and the expiratory muscles, with glottis closed. The automatic factors are relaxation of the internal anal sphincter and peristalsis of the rectum and pelvic colon. The impulse to evacuation probably arises only from distention of the rectum.

Constipation (over-long retention of feces) results in many persons, although not in all, in characteristic symptoms that have been generally attributed to autointoxication, but are probably more often due to nervous impulses and tonus gradient reversals set up as the mechanical result of fecal impaction.

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CHAPTER XXVII.

EXCRETION.

The Organs of Excretion.—The function of the special excretory mechanisms is to rid the circulating blood of all metabolic wastes other than carbon dioxide, and possibly on occasion some acetone (page 235), both eliminated by the respiratory tract. All these wastes (except cholesterol) are passed out in water solution, hence a loss of water from the body necessarily attends the excretory processes. The kidneys are the chief excretory organs. Supplementary to the kidneys are the ureters, the bladder and the urethra. Another excretory organ of importance is the liver, which discharges cholesterol and bile pigments *via* the bile duct into the intestine, whence they pass to the exterior as constituents of feces (page 427). The excretory function of the sweat glands is incidental to their main function of heat elimination (page 449).

THE KIDNEYS.

These organs make up about 0.4 to 0.5 per cent of the body weight in adults. Each is estimated to include some 4,500,000 capsules with accompanying convoluted tubules. There is no evidence that the kidney as such is under any sort of nervous control, although the bloodvessels of the organ have pronounced vaso-constrictor innervation, and clearly established, but less prominent, vaso-dilator innervation as well. The blood supply is described in Chapter XXI, page 355.

NORMAL URINE.

Human urine is a yellowish liquid with an average specific gravity of about 1.020, but varying widely from this average under different conditions described below. The daily quantity averages about 1200 to 1500 ml., although here again the range is wide, the volume varying on the whole directly with water intake and inversely with sweat secretion (page 436). Any increase in volume over the normal constitutes *diuresis*. The agency causing it is a *diuretic* (page 440). The reaction of urine is usually acid (page 166). The chief solid constituents are described in Chapter XIV.

Factors Governing Urine Formation.—The urine passing down the ureter is the composite product of a great and varying number of

tubules. The nature and amount of urine formed during any given time depends in part on the number of tubules in function during the time in question and in part on the activity of the individual tubules contributing to the total. The factors determining the number of glomeruli in function are not fully understood. In general, as already pointed out (page 356), the presence of vaso-constrictor substances in the blood cuts down the number, and the presence of vaso-dilator substances increases it. To what extent other factors enter remains to be discovered.

According to the theory of kidney function outlined in Chapter IX, the output of any individual tubule is the resultant of the following four processes: (*a*) Filtration through the capsular membrane; (*b*) active secretion of excretory substances; (*c*) selective reabsorption of reabsorbable solids; (*d*) reabsorption of water; the last three by the tubule cells. To account for the volume and composition of any given sample of urine one should know the quantity and composition of the liquid filtering from the glomeruli, the amount of each excretory substance added to this filtrate by active secretion, the amount of reabsorption of each reabsorbed constituent, and finally the quantity of water reabsorbed. Certain definite conditions govern each of the above. These conditions are understood only in part. A summary of present views regarding them is given in succeeding paragraphs.

Factors Governing Glomerular Filtration.—This topic is discussed in former chapters (pages 144 and 355), where the conception is advanced that glomerular fluid is produced by simple mechanical filtration under the driving force of the hydrostatic pressure of the blood. The capsular membrane is, however, impermeable to the plasma colloids, consequently the filtrate is non-colloid plasma, and the effective filtration pressure is glomerular blood-pressure less the osmotic pressure of the plasma colloids. The actual value of glomerular pressure is not known, although it is known to be somewhat higher than capillary blood-pressure. It probably rarely or never reaches 100 mm. Hg. normally. The effective osmotic pressure of the plasma colloids is somewhat less than 30 mm. Hg. (page 145); the force causing filtration is the difference between the above two values. The blood is viscous, hence filters with some difficulty; the capsular membrane interposes a certain frictional resistance to the movement of fluid through it; furthermore the *surface available* for filtration is both unknown and variable. It follows that the quantity of filtrate formed per unit of time could not be foretold, even though the effective filtration pressure were known. The evidence from diabetes insipidus (page 438) suggests that the filtrate may be on the average of the order of two to twenty times the volume of finished urine, or 4 to 25 liters per twenty-four hours. (A view urged by Cushny, and supported by various

other investigators, is that the filtrate is sixty or more times the volume of urine.) The amount varies, moreover, with every change in glomerular blood-pressure, as well as with every change in filtration surface (page 357).

Factors Governing Elimination of Secreted Urinary Constituents.— The secreted constituents include chiefly urea, the purin bodies, creatinine, potassium and ammonium sulphates and phosphates and miscellaneous compounds with relatively large molecules (dyestuffs and the like) introduced into the blood either experimentally or in the course of food ingestion or drug administration. It appears that the tubule cells have the property of withdrawing some of these materials actively from the blood. This implies that as they dialyze from the plasma into the cells they are set aside in some manner that prevents them from hindering further dialysis, thus they accumulate within the cells in higher concentration than in the plasma. Positive evidence has been obtained that certain dyes (phenol red) are concentrated in this manner in the kidney (Marshall and Crane) and also that purin bodies (urates specifically) are similarly concentrated (Folin, Berglund and Derick). Materials accumulated thus are subsequently passed on into the lumen of the tubule, completing the act of secretion. (In the dog, a species in which the circulating blood has remarkable destructive action on urates (page 237), these may accumulate in the kidney up to 0.2 per cent when injected rapidly into the blood stream, and be *returned to the blood again* as the urate concentration of the same falls, to be destroyed in turn.)

Urea and the inorganic sulphates and phosphates have not been certainly proved to be concentrated within the tubule cells, as a first step in the act of secretion, as are the dyestuffs and purin bodies described above. This difference has led various investigators to question whether urea and the phosphates and sulphates are actively secreted. These substances are, however, normally greatly contrated in urine (see table, page 147), and it is difficult to escape the conclusion that if the kidney has any secretory action at all these compounds are subject to it. Furthermore, the elimination of urea under various experimental conditions has been found (Bourquin and Laughton) to parallel closely that of uric acid, which undergoes preliminary concentration in the kidney (see above) and of ammonia, which is synthesized by the kidney cells (page 148) and would seem to be necessarily eliminated by secretion. Unless urea is secreted actively this parallelism is not easy to account for. It should be noted that preliminary concentration has not been proved to be an essential part of active secretion.

A very significant fact about the elimination of urea and the inorganic sulphates and phosphates is that the *rate of elimination*, in other words, the number of milligrams discharged per unit of

time, tends to be directly proportional to the concentration of the substances in the *blood plasma*, and quite independent of their concentration in the urine (Addis and associates). The secretory activity of the tubule cells is somehow adjusted to cause them to expel these substances at a rate proportional to their plasma concentration, even though in so doing quite different amounts of work have to be done to accomplish a given amount of secretion. If, as appears, these substances are not first concentrated in the tubule cells, they must be expelled into the gland lumina as fast as they enter the cells. If it be assumed that the cells function automatically and promptly to expel into the tubule lumina all the urea or phosphate to enter them, the diffusion gradient would vary at all times directly with the plasma concentration, making the rate of dialysis into the cells directly proportional to the same, thus fulfilling the situation found to exist. The fact that these substances escape in part by filtration from the glomeruli does not affect the quantitative relation between plasma concentration and elimination rate, since so long as other conditions remain constant any change in plasma concentration of a constituent that both filters out through the glomeruli and dialyzes into the tubule cells will affect the rate of both processes equally.

The ratio *milligrams excreted per hour* to *milligrams per* 100 *ml.* blood is reported to be the same for both urea and phosphate, *i. e.*, 54. Assuming a plasma urea concentration of 28 mg. per 100 ml. (page 236), this implies an hourly urea output in the urine of 1500 mg., a figure frequently found on direct urine analysis. Sulphates, which are apparently dealt with in the same way as urea and phosphates, have not yet had their ratio reported. It is important to bear in mind that maintenance of a constant ratio implies uniformity in number of functioning tubules; any condition leading to opening or closing of entire glomeruli in unwonted numbers disturbs the ratio in proportion (page 440).

Factors Governing Elimination of Reabsorbable Urinary Solids. – Glucose, amino-acids and the chlorides of sodium, calcium and magnesium are reabsorbed from the glomerular filtrate by certain of the tubule cells (evidence exists, advanced chiefly by Starling and Verney, that this reabsorption is accomplished by cells nearer the capsules than those that reabsorb water). The reabsorption is complete for each substance up to a definite limit (characteristic for each) known as its *threshold*. So long as the concentration in the filtrate is below the threshold only traces of the substance appear in urine. Whenever the concentration rises above the threshold, on the other hand, reabsorption is incomplete, the excess being eliminated.

The threshold for glucose is about 0.17 per cent. This is sufficiently above the normal sugar concentration of blood (0.10 to 0.12

per cent) to prevent sugar wastage except under conditions of pronounced sugar mobilization or when insulin is deficient (page 180). The threshold of amino-acid reabsorption appears to be slightly under the normal blood concentration of these compounds (about 0.005 per cent; page 181), since they occur in urine, but only in small amounts. The readiness with which deaminization occurs prevents amino-acids from accumulating in the blood to any extent, consequently they are never normally present in the glomerular filtrate in concentrations much above their threshold. The threshhold for NaCl reabsorption would appear to be below the concentration of this salt in plasma (about 0.6 per cent; page 251), since NaCl occurs constantly in normal urine. However, as already noted (see page 173), the elimination of NaCl is not to be explained so simply. In complete salt starvation the kidneys reabsorb NaCl so nearly to completion that the daily output may be only about one-hundredth the usual amount; this occurs with an almost imperceptible lowering of the NaCl concentration of the plasma, and by inference, of the glomerular filtrate. Furthermore, although increase in NaCl intake leads promptly to heightened elimination (suggesting the usual threshold relationship), the increase in elimination does not dispose of the entire surplus (page 173); considerable temporary storage occurs, and thereafter until the surplus has been excreted reabsorption fails to be quite as pronounced as usual, although again the NaCl concentration of plasma is not demonstrably or at most very slightly different from normal. An additional factor evidently enters, as yet unknown.

Factors Governing Reabsorption of Water.—Through the operation of glomerular filtration, selective reabsorption of threshold solids and active secretion of excretory substances the tubule lumens become charged with a liquid in which the dissolved constituents are in precisely the same relative proportion as in finished urine, but all in much greater dilution. The final act in urine formation is the reabsorption of 50 per cent or more of the water, raising the concentration to that of the finished urine.

In order for the tubule cells to reabsorb water actively, the blood (and, by inference, the glomerular filtrate) must contain post-pituitary hormone (page 206). So long as this condition is fulfilled reabsorption continues until finished urine is formed. Evidently the factors which set a limit to the extent of reabsorption determine both the concentration and the volume of the urine. They operate in such a way as to bring about two definite results: (*a*) To dissolve the excretory substances in such an amount of water that their concentration tends not to exceed a certain maximum; (*b*) to eliminate all excess water, either ingested or formed in metabolism, over and above the quantities lost by other channels of elimination (sweat glands, lungs and intestinal tract), so that the water content of the body remains uniform.

Various theories have been proposed to account for the reabsorption of water up to the limit indicated. The one outlined below is a modification by Chaussin of a conception of Ambard. The salient point in the theory is that an "obligate" volume of water attends the elimination of any given volume of substance. In other words, the kidney must discharge at least n molecules of water for every molecule or ion of dissolved excretory material. Reckoning the obligatory water with reference to the chlorides, phosphates and urea of the urine, it is found that enough water must be eliminated so that the combined concentration of these does not much exceed 0.9 molecular (this figure as given is corrected for ionization of chlorides).

Under ordinary conditions the water content of finished urine is found experimentally to be that which gives the urinary constituents approximately the above concentration, except during periods of over-absorption of water from the alimentary tract (page 159), when the excess water is rapidly eliminated and hence a more dilute urine is formed. The maintenance of an optimum concentration can be accounted for fairly well on an osmotic basis. The necessary conception is simply that the tubule cells tend to reabsorb water up to a limit set by a definite concentration of tubule fluid. This fluid starts as glomerular filtrate (plasma minus its colloids) with an osmotic pressure only slightly less than that of plasma itself. The active secretion of urea and of potassium and ammonium salts (page 147) raises the osmotic pressure. This is usually more than offset by reabsorption of NaCl and glucose, the resultant tubule fluid having an osmotic pressure lower than that of blood plasma, and much below the maximum at which the tubule cells cease to reabsorb water. Active water reabsorption, therefore, goes on until the maximum concentration is nearly or entirely reached.

The theory just outlined applies to urine formation when no excess of water is present. To account for the fact that overingestion of water leads regularly to formation of a dilute urine, some additional conceptions are necessary. A significant feature of the elimination of excess water is that it is very closely quantitative. When the body is in water equilibrium and is forming urine of optimum concentration the ingestion of as little as 150 ml. water has been observed to increase the volume of urine (diluting it to correspond), until approximately 150 extra milliliters were eliminated, when volume and concentration returned to normal. Ingestion of large surpluses may increase the rate of water elimination twenty to thirty times (Adolph). The excess water dilutes the blood plasma (and glomerular filtrate); the effect of the dilution is to lower the concentration to which the tubule cells tend to bring the finished urine. In view of the fact that active secretion of urea and of potassium and ammonium salts into the filtrate and active withdrawal of NaCl and glucose from the same obliges the

tubule cells to exercise their function of absorbing water upon a medium of different concentration from blood plasma to begin with, it is difficult to see on any osmotic basis how such slight dilutions of the glomerular filtrate as are effective can alter the activities of the water-absorbing cells as they do.

A suggestion that may prove to supply the correct explanation makes use of the properties of the postpituitary hormone as a regulatory factor of tubule-cell activity (page 206). The reader will recall that to this hormone is attributed a definite effect on urine volume explained as due mainly to a stimulating action on the tubule cells concerned with reabsorption of water. In brief, the more abundant the hormone, the more effectively do the cells take up water, and hence the less the volume of finished urine. Dilution of the glomerular filtrate necessarily lessens the concentration of postpituitary hormone in contact with the tubule cells. Assuming them to respond with great delicacy to changes in hormone concentration, it is conceivable that their reabsorbent power is thus cut down to an extent nicely adjusted to secure elimination of the excess water.

The mechanism as pictured above accounts for the observed variations in urine volume under most normal conditions. The formation of a concentrated urine when water intake is restricted is seen to be simply the action of the tubule cells in reabsorbing water up to the concentration maximum. The fact that ordinary urine is more dilute than this expresses the general tendency of persons with free access to water to ingest more than the necessary minimum.

Diabetes Insipidus.—In this disease, as already stated (page 146), a large volume of dilute urine is constantly formed. A daily elimination of as much as 26.5 liters is on record (Osler and McCrae: *Practice of Medicine*). The disturbance is confined mainly to water elimination. The solid constituents are given off in nearly normal total amounts, although necessarily in great dilution. The power of the tubule cells to reabsorb glucose and salts of sodium, calcium and magnesium is not materially affected; nor are the active secretions of urea and other secreted substances influenced, so far as can be judged. The most satisfactory explanation is that postpituitary hormone is greatly reduced in amount or wholly wanting. In experimental animals a condition essentially identical with human diabetes insipidus can be induced by extirpation of or injury to the posterior lobe of the pituitary. Conversely, marked relief, both in experimental animals treated as above and in human patients, is obtained by administering postpituitary extract (page 206).

Effects of Circulatory Changes.—In interpreting the effects of blood-pressure changes on urine formation care must be taken that the character of the blood flow *in the kidney* itself is being taken into

account. Thus a rise in general arterial pressure tends to augment kidney blood flow. But if the rise is due to peripheral vaso-constriction in which the kidney vessels share, as is the case whenever the constriction is due in whole or part to a flow of impulses over the splanchnic nerves, the kidney circulation instead of being augmented may be unchanged or even reduced. A fall in general arterial pressure necessarily lessens the blood flow through the kidney vessels, unless at the same time local dilation of these vessels is so pronounced as to reduce their resistance disproportionately, in which case more blood than usual is diverted into them. The relation of the glomerular vessels to the kidney circulation in general is such that the more abundant the blood flow the higher the glomerular pressure. (For details, see page 355)

With the above facts in mind, the relation of kidney blood flow to urine formation may be stated as follows: Whenever the pressure of blood in the glomeruli falls to or below 30 mm. Hg. filtration ceases and no urine is or can be formed (page 433). Whenever the glomerular pressure rises above this minimum filtration begins. The filtrate itself is of normal composition, *i. e.*, blood plasma minus its colloids. The *volume of filtrate* per capsule varies directly with glomerular pressure; consequently a slight pressure rise above the level of no filtration yields a small volume of filtrate, less at first then the normal yield of finished urine. The various secretory constituents are added to this filtrate in proportion to their concentration in the blood flowing through the tubule vessels (page 435). The fact that the filtrate is scanty does not affect this action so far as known, although it may be that anoxemia of the tubule cells, due to insufficient blood flow to them, reduces their secretory activity. Unless the latter effect prevails, the proportion of urea to NaCl would be expected to be higher than in the normal tubule fluid. Whether reduced volume of filtration is attended by reduced relative reabsorption of NaCl, so that the final concentration of the latter approaches normal, is not known. Reabsorption of water presumably occurs as usual until the tubule fluid becomes of optimum concentration. The net result to be anticipated is that each tubule will produce a smaller volume of finished urine, probably richer in urea and possibly poorer in NaCl, than at normal glomerular pressures.

As glomerular pressure rises well above the filtration threshold the volume of glomerular filtrate increases and with it the volume of finished urine, although not in direct proportion. The factors governing urine volume (page 432) are, in fact, quite independent of volume of filtrate, provided the latter is at all adequate, consequently for a considerable range in filtration volume above some minimum level urine volume is presumably fairly constant. If glomerular pressures rise above the upper limit of this range the

volume of filtrate becomes so great that the flow of fluid down the tubules is too rapid for the reabsorption processes to keep pace with it. This applies particularly to NaCl and water, the two constituents that are ordinarily reabsorbed in quantity. The finished urine is consequently larger in volume and more dilute than normal, and shows an absolute increase in NaCl. The total elimination of other solids per unit of time is not much affected. All the constituents are in less concentration in proportion to the increase in unabsorbed water.

The relationships described above for lessened glomerular pressure apply equally to the situation in which some of the capillaries in individual glomeruli close, reducing but not stopping the flow of blood through them (page 357). The effect is to lessen the filtration surfaces, which cuts down the volume of filtrate just as does reduction in filtration pressure. A secondary effect of closure of part of the capillaries is to lessen the blood flow through corresponding convoluted tubules, since all tubule blood flows first through glomeruli (in mammals). Whether this lessening has any effect on tubule function is not known.

Glomeruli may go out of or into function in entirety (page 356). The immediate effect is to change the total volume of urine without affecting its composition. In the long run, however, changes in composition may also be brought about. Thus if the number of functioning glomeruli were to decrease to such a point that the elimination of urea and other secreted products became less rapid than their synthesis in the body the plasma concentration of these substances would rise and their rate of elimination per tubule increase to correspond (page 435); conversely a marked increase in number of functioning glomeruli might result temporarily in secretion of these substances faster than produced, leading to a drop in their rate of elimination per tubule.

Diuresis.—Any marked increase in urine volume above normal constitutes a *diuresis*. There are three main types. *Circulatory* diuresis is an increase in volume due either to increase in number of functioning glomeruli (see above) or to a rise in glomerular pressure, or more commonly to both together. The diuretic action of caffein and other capillary dilators is thus explained (page 356). *Postpituitary diuresis* is due to effects produced through the postpituitary hormone. A transient diuresis, really of the circulatory type, may be due to selective stimulation of the efferent glomerular vessels by the hormone, thus raising glomerular pressure (page 206). The more common type is due to decrease in or absence of the hormone and consequent partial or total failure of reabsorption of water (page 206). A significant feature of both circulatory and postpituitary diuresis is that they have no relation to the excretory needs of the body. They always sweep out some constituents with undue rapidity, necessitating either augmented intake, as of water

in diabetes insipidus (page 438), or a subsequent period of lessened elimination to permit reëstablishment of equilibrium.

The third type, designated as *physiological diuresis*, is an augmentation in urine volume due to the presence of excretory substances in larger than normal amounts. If the substance is water it is eliminated in excess, as discussed above (page 437). The ingestion of NaCl or urea in sufficient quantities to raise the plasma concentration of either results in increased elimination which will induce diuresis unless a sufficient water diuresis is already in progress. Any procedure which raises the glucose concentration above the threshold has the same effect. The reason is simply that water tends to be eliminated in sufficient amount to keep the total concentration of the urine at about 0.9 molecular (page 437); hence, if surplus water happens not to be available in the blood stream the tissues are drawn upon. When large amounts of these substances are administered experimentally very copious diureses are seen. As in diabetes insipidus the depletion of the water stores of the body induces thirst (page 159), leading to augmented intake.

THE URETERS.

These tubes connecting the kidneys with the bladder are essentially smooth muscle tubes, displaying the characteristic properties of such structures. They show regularly recurring peristaltic waves, by which the urine as it accumulates in the kidney hiluses is propelled to the bladder. The waves are presumably aroused and coördinated, as in the small intestine, through the intrinsic nerve plexuses (page 394). They occur at the rate of 3 to 6 per minute, and are stated to move with a velocity (in rabbits) of 20 to 30 mm. per second. The chief stimulus by which waves are set in motion appears to be distention due to pressure of accumulating urine in the upper ends of the tubes (Satani).

The ureters have double autonomic innervation, differing, however, from the typical (according to Satani), in that excitation may be evoked both by sympathetic (splanchnic nerve) and parasympathetic (pelvic nerve) stimulation, while inhibition is evoked by stimulation of a special set of sympathetic fibers (from the inferior mesenteric ganglion).

The ureters enter the bladder obliquely through the wall of the latter; any considerable rise in pressure within the bladder squeezes the ureters shut; thus back flow is effectively prevented.

THE BLADDER: MICTURITION.

The bladder is a smooth muscle sac capable of change in capacity from zero (or virtually that) to above 300 ml. Increase in capacity is brought about by relaxation of tonus in very much the same manner as described for the stomach (page 395). However, as

urine accumulates in the bladder the pressure of the walls on the contents tends to rise, slowly at first, but mounting as the walls distend, until when about 250 ml. are present the tension ordinarily amounts to about 150 mm. H_2O (11 mm. Hg.). The bladder is prevented from emptying itself meanwhile by strong tonus of the *sphincter trigoni*, the internal sphincter of the bladder, composed of smooth muscle.

At about the above pressure rhythmic contractions of the bladder musculature begin. These are intrinsic in origin and production, occurring in bladders cut off entirely from connection with the central nervous system. In an organ thus isolated they become progressively more marked as entering urine continues to distend the walls, until the tonic resistance of the internal sphincter is overcome, when expulsion of urine occurs. This continues only until the pressure is reduced below the stimulation level. Hence isolated bladders do not empty themselves completely. In the intact organism the same tension that initiates rhythmic contractions stimulates afferent nerves, giving rise to feelings of uneasiness and desire for micturition. If the occasion is propitious certain accessory factors of micturition are called into play, chiefly reflexly, although in human beings beyond infancy in part volitionally, and the bladder is completely evacuated. These factors include definite inhibition of the smooth muscle internal sphincter; relaxation of the urethral walls and of the striated muscle structures that act as external sphincters, *i. e.*, the *sphincter urogenitalis* and (in males) the *bulbocavernosus muscle;* active contractions of the muscles of the bladder walls themselves (the *detrusor urinæ*); and usually contractions of the abdominal muscles, compressing the pelvic contents. The total pressure brought to bear may amount to 100 mm. Hg. If the spinal cord is cut across above the lumbar region the entire act occurs as a pure spinal cord reflex.

Micturition may be inhibited volitionally. When this occurs the external sphincters are excited to stronger contractions than normal. Usually contractions of the perineal muscles are also aroused to reinforce the action of the sphincters. As the inhibition is sustained the tonus of the bladder is readjusted, the pressure on the contents diminishing. The desire then passes off, to be renewed later as the former pressure is reëstablished at a higher level of distention.

Relation of the Central Nervous System to Micturition.—The bladder and its smooth muscle accessories act like other smooth muscle structures in responding to autonomic nervous influences. Ordinary evacuation is due to parasympathetic discharges; over the nervi erigentes (page 750) in dogs; over fibers of the pelvic plexus in man. Under conditions of nervous strain the pressure usually increases sharply, an effect of sympathetic discharges, arousing

desire for micturition, even though only a few milliliters of urine may be present. Such very copious discharges over the sympathetic system as attend extreme fright thus typically cause reflex evacuation of the bladder, sometimes without the knowledge of the victim.

In children sensory irritation, particularly of the pelvic region, arouses reflex micturition readily. In adults influences inhibitory to the act may dominate completely over conditions tending to induce it. Thus self-consciousness may make micturition impossible, even when one is in acute distress from overdistention of the bladder. Furthermore, an adult may dream of evacuating the bladder and wake to find it greatly overdistended, but the sphincters holding effectively.

Summary.

The *kidneys* eliminate daily 1200 to 1500 ml. of urine, more or less, the volume varying directly with water intake and inversely with sweat secretion. The specific gravity averages about 1.020, but varies widely from this average.

The *nature and amount of urine* depend in part on the number of tubules in function and in part on the activity of individual tubules. The latter factor is the resultant of four processes: *a* Filtration through the capsular membrane; *b* active secretion of excretory substances; *c* selective reabsorption of reabsorbable solids; *d* reabsorption of water.

The volume of *glomerular filtrate* cannot be determined directly. It is estimated to amount to two to twenty times the volume of finished urine (the theory of Cushny postulates a much larger volume of filtrate).

The *secreted* urinary constituents appear to fall into two categories according as they are concentrated within the tubule cells before being expelled or not. Dye-stuffs, such as phenol red, and the purin bodies have been shown to be concentrated; urea, phosphates and (presumably) sulphates appear not to be concentrated. The latter group show a constant ratio of milligrams excreted per hour to milligrams per 100 ml. blood. For urea and phosphate the ratio is 54.

Glucose, amino-acids and the chlorides of sodium, calcium and magnesium are reabsorbed completely by the tubule cells up to a *threshold* concentration. The threshold for glucose is about 0.17 per cent; for amino-acids probably slightly below their plasma concentration; for NaCl near its plasma concentration (NaCl reabsorption appears to be governed in part by other unknown factors additional to its threshold relationship).

Both the total concentration and the volume of urine are deter-

mined finally by the extent of water reabsorption by the tubule cells. The limit to water reabsorption appears to be the attainment of a certain osmotic pressure in the tubule fluid. When no surplus water is present to be discharged the urine tends to approach optimum concentration. Excess water is quantitatively eliminated, keeping the water content of the body uniform.

In *diabetes insipidus* all kidney functions appear to proceed nearly normally except reabsorption of water, which is largely or wholly suppressed. Evidence indicates the postpituitary hormone to be deficient or wanting.

The *volume of filtrate* per open capsule varies directly with the pressure of blood in the *glomerular capillaries*. Glomerular pressure rises with general arterial pressure, except when vaso-constriction of the kidney arterioles occurs simultaneously; also with local vaso-dilatation of the kidney vessels, provided general arterial pressure is not disproportionately reduced at the same time. Filtration occurs only at glomerular pressures higher than about 30 mm. Hg. The relation of volume and composition of finished urine to volume of filtrate is not thoroughly known. It appears that when filtration is particularly copious reabsorption of NaCl and water fails to keep pace, leading to formation of a dilute urine with increase in absolute NaCl elimination.

Diuresis of *circulatory origin* is due either to increase in number of functioning glomeruli or to rise in glomerular pressure. Capillary dilators, like caffein, are thought to induce diuresis thus.

Postpituitary diuresis (non-circulatory) is attributed to deficiency of hormone, whereby reabsorption of water is cut down.

Physiological diuresis is due to the presence in the blood of excessive quantities of excretory substances. As these must be eliminated in concentration not much exceeding a given optimum, large amounts of water accompany them. Surplus water is itself inducive of physiological diuresis.

The *ureters* show peristaltic waves recurring three to six times per minute; the inciting cause is thought to be distention with urine. The musculature is subject to both excitatory and inhibitory stimulation through the autonomic system.

The *bladder* is a smooth muscle sac which on becoming distended with urine (to about 250 ml. ordinarily) reacts by contracting rhythmically. In intact organisms desire for micturition is aroused also. The bladder is under control of the autonomic system; consequently readjustments of tension with attending increase in or disappearance of desire for micturition may occur, due to various affective states and independently of the amount of urine present.

Normal *micturition* involves inhibition of the smooth muscle internal sphincter and the striated muscle external sphincter or sphincters, active contractions of the muscles in the bladder walls, and usually contractions of the abdominal muscles as well.

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(See also Bibliography at end of Chapter IX.)

CHAPTER XXVIII.

TEMPERATURE REGULATION.

Statement of the Problem.—Warm-blooded (strictly speaking *homothermous*) animals display two characteristic temperature phenomena: In the first place, they produce heat continuously and rapidly; in the second place, the heat produced is dissipated at virtually the same rate as formed, so that except for minor fluctuations, and the marked drop attending hibernation in some forms, body temperature remains nearly uniform during health. This balance between heat production and heat dissipation is maintained in an environment which varies widely from time to time in heat receptivity, mainly through changes in temperature; in part, however, through humidity changes. The problem is to adjust heat loss to heat production in such fashion that the temperature of the body cells stays nearly constant at approximately the optimum level (page 156), *i. e.*, between 35° and 43° C. (in man, 37° C.; 98.5° F.).

Heat Transfer Within the Body.—Different tissues carry on basic metabolism at different levels and with different degrees of efficiency (page 59); moreover, functional metabolism occurs at quite irregular intervals and in different tissues at different times. The resulting tendency of the tissues to take on widely different temperatures is successfully counteracted by the circulating blood, which has the high heat capacity characteristic of water, and in its rapid flow absorbs heat from any tissues warmer than itself and imparts heat to any that are cooler, thus keeping all the internal tissues nearly equal in temperature. Furthermore, in its flow through the heat dissipating structures (skin mainly) it parts with as much heat as it takes up in the tissues, keeping the body temperature as a whole from rising or falling, except slightly and, under normal conditions, transiently.

THE HEAT CENTER.

The fact that any warm-blood animal maintains a fairly definite temperature, *to which its body will return* after a period of temperature rise, as in fever, or after a period of low temperature in hibernating mammals, proves the existence of a "thermostat" mechanism of some sort. Furthermore, the thermostat is "set" at one temperature in most mammals, and at another, higher one, in

birds. According to the older views, the body as a whole was supposed to function as thermostat. Evidence has accumulated of late years, however, that a localized area of the brain, near the corpus striatum, is the actual thermostat. This area is designated the *heat center*.

Influences Affecting the Heat Center.—The heat center appears to have the same general character as other "vital" centers (page 131). Like other centers, it functions by discharging streams of nervous impulses over the nervous system. The activity of the center itself is determined, in turn, by influences brought to bear on it either directly through the blood stream or in the play upon it of afferent nervous impulses originating in various receptors.

In its capacity as thermostat the heat center responds definitely to changes in the temperature of the blood flowing through it. Whenever blood temperature rises the discharges of the center are such as to cause bodily readjustments favorable to increased heat dissipation, thus tending to lower blood temperature to its normal level. Whenever blood temperature falls, on the other hand, the center acts on peripheral structures in a manner favorable to reduced heat loss, and hence to restoration of the former heat level.

The main channel of heat elimination is the skin. Furthermore, the skin is the only part of the body directly exposed to the environment, hence the only part whose temperature tends to rise and fall directly as the external temperature rises and falls. A very interesting feature of the action of the heat center is that it *anticipates* changes in actual blood temperature by reacting equivalently to changes in skin temperature. Thus a lowering of skin temperature excites receptors of cold (page 518); the resulting play of afferent impulses on the heat center evokes the same sort of discharge as lowering of blood temperature itself would. Conversely, a rise in skin temperature stimulates receptors for warmth (page 512), thus setting in play afferent impulses tending to evoke the type of activity of the center by which heat dissipation is favored. Since changes in skin temperature would inevitably lead, if uncompensated, to corresponding changes in blood temperature, it is evident that these reflexes serve a useful purpose.

Conditions to be Met in Temperature Regulation.—Before proceeding to discussion of the bodily readjustments evoked by the heat center, and the way in which they act to keep body temperature uniform, the conditions under which the mechanism must work may be called to mind. As already noted, the amount of heat to be dissipated is determined in the main by other considerations than the need of keeping the temperature constant. The level of basal metabolism appears to depend primarily on the quantity of hydrogen transporters present in the tissues (page 49), although as pointed out in Chapter XXIX, there is a curious quantitative

relationship between basal heat production and body surface. The heat yield of functional metabolism is essentially that of muscular activity, which tends to be adjusted somewhat to the external temperature, but in the nature of the case cannot be so adjusted invariably, hence the mechanism of temperature regulation must function on occasion to dissipate large quantities of heat into an environment whose heat-receiving capacity is relatively low.

The maximum drop in external temperature is so extreme outside the tropics that the human body, with its naked skin, would fail to adjust itself successfully were the automatic mechanism for temperature regulation not supplemented by intelligent measures. The effect of these, which include artificial heat, shelter and the blanket of non-conducting air kept next the skin by the clothing, is both to mitigate external conditions materially and to adjust them to variations in heat production associated with different degress of bodily activity.

Prevention of Temperature Fall.—A drop in blood temperature is a certain indication that heat is escaping from the body faster than it is being produced within it. Likewise, a fall in skin temperature is a sign that the same will happen if not prevented. The reaction of the heat center to either of these conditions brings about a series of bodily changes tending first to lessen heat loss and second to augment heat production; the latter mainly when conditions are such that simple prevention of heat loss will not suffice to maintain normal body temperature. The following readjustments make up the first category: (*a*) Skeletal muscle reflexes reducing the area of exposed surface (the characteristic "huddling" seen in lower animals and in human beings when too thinly covered in bed); (*b*) discharges over the sympathetic system, causing cutaneous vasoconstriction, and hence less escape of heat from blood flowing through the skin; (*c*) a reduction in blood volume, presumably significant in that it permits the cutaneous circulation to decline without excessive engorgement of the internal vessels. The precise mechanism by which fluid is transferred from the vessels to the tissue spaces and cells under the stimulus of lowered temperature is not known; (*d*) lessening of sweat secretion. This is not thought to be due to active discharges from the heat center; it appears rather to indicate a decline in the potency of influences which cause the center to discharge secretory impulses to the sweat glands.

In the second category, *i. e.*, augmentation of heat production, are: (*a*) An increase in basic metabolism due to outpouring of adrenin (Cannon). This action appears to be the result of sympathetic discharges to the adrenal glands. A transient increase of heat production of as much as 25 per cent has been reported in man, following administration of 750 ml. of water at 1° C. (a "heat

liability" of 574 Calories per kilo body weight). The peak occurred twelve to twenty-five minutes after ingesting the cold water. In experimental animals in which the adrenals were rendered inactive the phenomenon did not occur; (*b*) reflex increase in functional metabolism of skeletal muscles, taking first the form of heightened tonus (resisting the cold) and second of shivering. External temperature around 14° to 15° C. usually evoke this reaction. However, in animals deprived of adrenin shivering occurs at slightly higher temperatures; (*c*) volitional muscular activity, which may be as vigorous as occasion demands. Whether the heat center is concerned in the discharge of impulses into the higher brain centers by which volition activity is initiated cannot be said at present.

Prevention of Temperature Rise.—A rise in temperature either of blood or skin sets in operation discharges from the heat center favorable to increased heat dissipation. These are: (*a*) Reflex exposure of maximum body surface (the outstretched body of animals in warm weather); (*b*) hyperpnea (the panting with out-hanging tongue, whereby fur-bearing animals facilitate discharge of water vapor from the lungs); (*c*) cutaneous vaso-dilatation, securing maximal blood flow through the skin, and hence maximal discharge of heat by radiation and conduction; (*d*) excitation of the sweat glands, leading to out-pouring of much water to the surface, with corresponding discharge of heat, provided evaporation occurs; (*e*) increase in blood volume, significant both as a means of preventing the cutaneous vaso-dilatation from depleting internal organs unduly of blood, and as a provision of ample water for discharge by the sweat glands. The increase in blood volume probably does not prevent some depletion of internal organs, since the kidneys eliminate less water as the sweat glands discharge more (page 436); the depletion is often marked enough, moreover, to arouse sensations of thirst (page 159); (*f*) voluntary discontinuance of muscular exertion.

At ordinary room temperatures probably about three-quarters of the heat produced in the human body is dissipated by radiation and conduction from the skin, and one-quarter by evaporation of water discharged from lungs and sweat glands (Vierordt). Evaporation of water from the skin is about double that from the lungs. Warming the expired air accounts for about 3 per cent of the total heat loss. At higher surrounding temperatures the proportion shifts, relatively more heat escaping by evaporation and less by radiation and conduction.

SWEAT SECRETION.

The sweat glands, estimated to number between 2,000,000 and 3,000,000 altogether, are excited to secrete by discharges over the sympathetic system. The volume of secretion per unit of time is

highly variable; it is estimated to range from a minimum of about 700 ml. per twenty-four hours to a maximum of three times that figure or more. Whether volume changes are due to changes in number of active glands or in output of individual glands is not known.

The composition of sweat does not change materially with changes in total volume; slight differences are noted, however, in sweat collected from different skin areas. In prolonged sweating the concentration increases somewhat. The hydrogen-ion concentration also falls appreciably. These changes correlate with accompanying changes in the blood.

In the inactive body exposed to high external temperatures the quantity of sweat is a linear function of the "effective" skin temperature (Adolph). The linear relationship begins to appear at about 90° F. The inference is that as the limit to heat dissipation by conduction and radiation is approached the discharges of the heat center achieve their maximal vaso-dilator effect, and further increases in intensity of discharge can produce results only by augmenting sweat secretion.

All the skin changes induced by discharges from the heat center operate harmoniously to favor or impede heat dissipation. The efferent path to the sweat glands is, however, over the sympathetic system, while the vaso-dilator path is parasympathetic (or antidrome, page 334). The sympathetic vaso-motor connections being constrictor (page 131), it follows that generalized sympathetic discharges, as in severe pain or major emotions (page 735) induce sweat secretion and cutaneous vaso-constriction simultaneously. Thus the phenomenon of "cold sweat" is accounted for.

PHYSIOLOGICAL TEMPERATURE RISE.

Surrounding temperatures higher than that of the normal body (98.5° F.) occur frequently or occasionally in most parts of the tropic and temperate zones. Heat loss by radiation and conduction is necessarily *nil* at such times. Sweat secretion and evaporation are correspondingly augmented. However, the efficacy of the latter mechanism depends on the relative humidity of the air. Whenever this mounts to 100 per cent heat dissipation by evaporation ceases. Fortunately both extreme conditions seldom occur together. They occasionally approach doing so in some localities, however, to the great discomfort of the inhabitants. Some rise in body temperature is inevitable under such circumstances. When heavy manual labor is performed at high temperatures, as happens of necessity in some industries, a temperature rise of as much as 2° F. may occur during every work period. A simple method of causing temperature to rise experimentally is to immerse the body

to the neck in water at body temperature. If the water is kept from cooling body temperature mounts rather rapidly. A significant fact is that the disagreeable sensations characteristic of ordinary fevers are experienced by the subject, showing these sensations to be due largely to the rise of temperature *per se*, rather than to the toxins to which the fever is due.

FEVER.

The explanation of the temperature rise and subsequent maintenance of supernormal temperature characteristic of most acute infections is not altogether certain. A conception seeming to agree reasonably well with the known facts is based on a suggestion of Woodyatt, that the primary action of the disease toxins on the body is to increase the affinity of the protoplasmic colloids for water. The immediate result is an augmentation of cell water at the expense of blood (the tissue spaces having little capacity for change in contents). The decrease in blood volume is assumed to affect the cutaneous circulation particularly, leading to a cooling-off of the skin. But when skin temperature falls afferent impulses are set in motion which play upon the heat center in a manner to cause it to function as heat conserver (Barbour). In other words, the center is warned of impending excess heat loss when none really impends. The ensuing discharges from the center (listed on page 448) lessen the heat-dissipating capacity of the body, and metabolism being little altered, cause its temperature to rise until the heat loss becomes great enough in spite of the conserving reactions to balance heat production, when the temperature becomes stationary. Since one phase of the heat-conserving reaction is decrease in blood volume, the initial effect of the disease toxin is accentuated. The chills and pallor that attend early stages of fever are readily explained according to this view, as is also the scanty sweat secretion.

There is increased basic metabolism in most fevers after they are once under way, but this in itself cannot account for the temperature rise, inasmuch as the total metabolism of a person in bed, even with a high fever, is much below that of a healthy individual doing heavy manual work. The temperature rise is itself sufficient cause for an increase in metabolism, since metabolic activity in general tends to vary directly with the temperature (page 462).

Summary.

In *warm-blooded* (*homothermous*) animals heat is produced continuously and rapidly, and the dissipation of heat from the body balances heat production in the body, thus uniform body temperature is maintained.

The swiftly flowing *blood transfers heat* from warmer to cooler

regions within the body, thus keeping all interior structures at nearly equal temperatures. The blood also *conveys excess heat* to the surface for discharge to the exterior.

The maintenance of constant body temperature implies the presence of a *thermostat* mechanism. An area in the brain near the corpus striatum, the *heat center*, is thought to function in this capacity.

The heat center is influenced directly by *changes in blood temperature*, and reflexly by *changes in skin temperature*. Temperature rise in blood or skin sets in play discharges from the center tending to promote heat dissipation. Temperature fall has the opposite effect.

Heat production in the body is a *function of total metabolism;* hence varies widely and irregularly from time to time. The *heat receptivity* of the environment is also widely variable, changing mainly with changes in external temperature, but in part with changes in relative humidity.

The potential extremes are greater outside the tropics than the naked human body can meet. Hence the *physiological heat-regulating mechanism is supplemented in man* by intelligent use of artificial heat, shelter and clothing.

The heat center reacts to *temperature fall* by discharges tending: (1) To lessen heat loss, and (2) to augment heat production. The reactions in the first category are: (*a*) Reduction of exposed body surface; (*b*) cutaneous vaso-constriction; (*c*) reduction in blood volume; (*d*) lessening of sweat secretion. The reactions of the second category are: (*a*) Increase in basic metabolism due to outpouring of adrenin; (*b*) reflex increase in functional metabolism by heightened muscular tonus and shivering; (*c*) volitional muscular activity.

The heat center reacts to *temperature rise* by inducing: (*a*) Exposure of maximum body suface; (*b*) hyperpnea (particularly significant in fur-bearing animals); (*c*) cutaneous vaso-dilatation; (*d*) augmented sweat secretion; (*e*) increase in blood volume; (*f*) voluntary discontinuance of muscular exertion.

Sweat is of nearly uniform composition but variable volume. The secretion is under the control of the sympathetic system. Whether changes in volume are due to excitation of different numbers of sweat glands or to excitation of individual glands to different extent is not known. At high external temperatures the quantity of sweat (in the inactive body) is a linear function of the "effective" skin temperature.

Generalized sympathetic discharges induce sweating and cutaneous vaso-constriction simultaneously. Thus "cold sweat" is explained.

Physiological temperature rise occurs when external conditions make adequate heat dissipation impossible at normal body tem-

perature; heavy manual labor at high external temperature is particularly apt to induce some temperature rise.

Fever is explained reasonably well on the view that disease toxins act to increase the affinity of protoplasmic colloids for water, with the result that blood volume is reduced. The effect is assumed to be localized mainly at the body surface, leading to its cooling. Thus heat-conserving reactions are set off unrelated to the actual heat equilibrium, necessarily resulting in temperature rise.

The increased basic metabolism of fever is looked on as a result of the temperature rise rather than as a cause.

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CHAPTER XXIX.

CALORIMETRY AND DIETETICS.

Significance of Metabolism Data.—Data on the energy output of the intact body, at rest or in various degrees of activity, are of great value in physiology and medicine. The resting (basal) metabolism of the normal organism is automatically adjusted within quite definite limits; consequently if the limits are known any given individual can be assigned on test to a proper category; his metabolism is either subnormal, normal or supernormal.

Metabolism measurements are particularly instructive in connection with disturbances in hormone or vitamin function (Chapter XII); they have value, however, in any problem in which the energy turnover of the body is a factor. Thus the whole matter of the efficiency of the animal body as a machine, either for doing mechanical work, as in industry, or for converting farm produce into meat, as in animal husbandry, involves information as to the energy output under various conditions.

Energy Units.—Since the entire energy yield of the resting body appears at the exterior as heat, and since the heat equivalents are accurately known for chemical and mechanical energy transformations, the usage has arisen for stating all energy values in heat units. The basic unit is the *gram calorie, i. e.*, the amount of heat required to raise the temperature of 1 gm. of pure water from 14.5° to 15.5° C. This unit is frequently referred to as the *microcalorie* to distinguish it from the *large calorie*, a unit exactly one thousand times as great, for which the word calorie by itself is commonly used. The latter unit is of a more convenient size than the microcalorie for the data of animal calorimetry, and is the one generally employed. Some authors capitalize the word when they have large calories in mind, but many do not, and the reader must take care to ascertain from the contex which unit is meant.

BASAL METABOLISM IN RELATION TO BODY SURFACE AND PROTOPLASMIC MASS.

In mammals there is a fairly constant relationship between basal metabolism and body surface. When this fact was first called to the attention of investigators (Rubner) attempts were made to interpret it in terms of Newton's "law of cooling," according to which rate of cooling is a function of the surface of the cooling body. However, further investigation has made it clear that metabolism

is governed by other factors than the tendency to lose heat. The single factor which would appear, more than any other, determinative of basal metabolic rate is the total quantity of available hydrogen transporters (page 49). This quantity is at present unmeasurable, however, and no reason is known why it should bear any relation *per se* to body surface. Benedict suggests *mass of active protoplasm* as the nearest practical approach to the rate-determining factor. Indirect evidence (as that nitrogen elimination in cattle is proportional to body surface) permits the observed surface relaship to be reconciled with the protoplasmic mass conception by considering body surface to be directly proportional to protoplasmic mass.

According to Rubner's original estimate, the basal heat production in mammals is approximately 40 Calories per square meter of body surface per hour. As a matter of fact actual tests on mammals ranging in size from mouse to horse give results agreeing remarkably with the above estimate. More exhaustive tests have been made on man, however, than on any other form, and these have shown the heat yield per unit of body surface not to be a fixed constant, but to vary with age and sex. It is relatively low at birth and for a few weeks thereafter (29 to 33 Calories per sq. m. per hour), when the infantile nervous system is functioning imperfectly and skeletal muscle tonus is largely absent. It rises to a maximum by about the end of the second year, when nervous function is fully established and growth metabolism (necessarily included in determinations of basal metabolism) is active. Thereafter there is a continuous decline as age advances, particularly marked as the juvenile period reaches its end. Metabolism is somewhat higher in males than in females at all ages. Actual average data are given in the accompanying table.

TABLE OF STANDARDS OF NORMAL BASAL METABOLISM.

Average Calories per Hour per Square Meter of Body Surface.

Age, years.	Males.	Females.
8– 9 incl.	54.0	54.0
10–11	51.5	50.0
12–13	50.0	46.5
14–15	46.0	43.0
16–17	43.0	40.0
18–19	41.0	38.0
20–29	39.5	37.0
30–39	39.5	36.5
40–49	38.5	36.0
50–59	37.5	35.0
60–69	36.5	34.0
70–80	35.5	33.0

Calculation of Body Surface.—The irregular surface of the body cannot be measured with any degree of accuracy except by a tedious

and difficult process (DuBois and DuBois). Efforts have accordingly been made to establish formulæ by which the surface can be calculated with reasonable accuracy from bodily measurements easy to obtain.

Of the various formulæ proposed, the one developed by DuBois and associates, and known commonly as the *DuBois standard*, is as satisfactory as any and is in common use. This formula is: $A = W^{0.425} \times H^{0.725} \times 71.84$; in which A is the surface area in square centimeters, W the weight in kilograms and H the height in centimeters. For a man of average weight and stature solution of this equation gives a body surface of approximately 1.8 sq. m. For convenience a DuBois chart, showing the calculated surfaces for various weights and heights is given in Fig. 49.

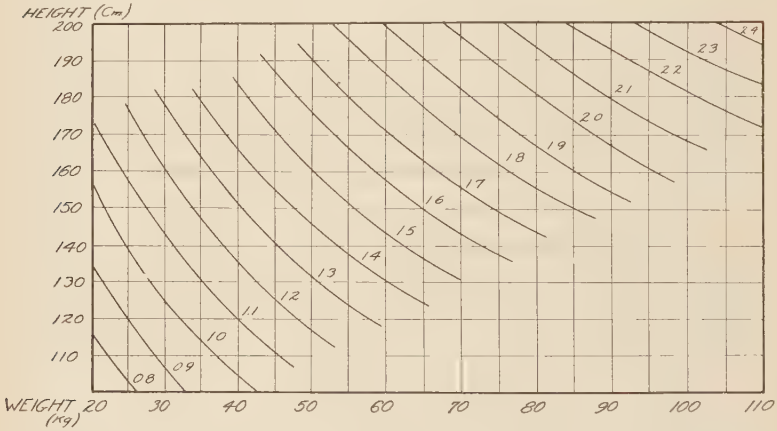

FIG. 49.—Du Bois body-surface chart. Curved lines represent areas in square meters. Heights are in centimeters and weights in kilograms.

BASAL METABOLISM.

The value for average body surface just stated, multiplied by 39, the mean heat yield per square meter per hour in males as set down in the table above, gives a round-number basal metabolism in adult males of 70 Calories per hour, or 1700 per day. The conditions under which this metabolism level is realized in practice are: The absence of absorption from the alimentary tract; complete muscular and mental repose (the subject to be awake, however); twenty to forty minutes of absolute rest immediately prior to the beginning of the test; a state of comfortable warmth but no departure of body temperature from normal.

Metabolism Measurements, Direct Calorimetry—The validity of the above or any other calculated metabolism data depends on experimental proof that the heat yield per square meter per hour is

actually as stated in the table. There are three distinct methods by which such proof may be had. The only entirely satisfactory method in theory is to enclose the subject in a *calorimeter* and measure his heat yield directly. This method is exceedingly difficult in practice. It has been applied to human beings on a large enough scale, however (Atwater; Atwater and Benedict) to afford ample proof that the more convenient methods described below actually give correct results. The practical difficulties with direct calorimetry in physiology are wholly technical, arising from the large size of the apparatus, the fact that the subject must breathe, and the continuous discharge of water vapor from the body surface. Not only must the heat given off to the calorimeter itself be accurately determined, but also that carried off in the air passed through the apparatus, either as raised air temperature or as water vapor.

Indirect Calorimetry.—A second method is to determine the energy value of the ingested food and of the excreta, and by difference the energy transformations in the body. The chief value of this method is obviously as a means of demonstrating that the energy displayed in the body is actually obtained, under normal nutritive conditions, from the food. It is inapplicable when body weight is changing.

The third method, adopted for practically all routine work on account of its convenience and wide applicability, consists of determining the oxygen consumption and carbon-dioxide output, and computing the fuel consumption, and hence the energy, therefrom. Two general types of apparatus are in use, a *closed-circuit* and an *open-circuit* type.

In closed-circuit types the subject breathes into and from a closed gas-tight system from which CO_2 is withdrawn as it accumulates and to which O_2 is added as consumed. The CO_2 is ordinarily absorbed by soda lime or other CO_2 absorbent, and the quantity determined by the gain in weight of the absorbent (obviously errors due to water vapor must be avoided). Oxygen is admitted from a storage tank, passing on its way through an accurate gas meter by which the quantity is registered. Since the CO_2 determinations are gravimetric and the O_2 determinations volumetric changes in gas volume due to shifts in temperature and vapor pressure affect only the latter; consequently, great care and expert manipulation are necessary to avoid distorted readings.

In open-circuit types the subject inhales pure air and exhales into a receptacle which is either large enough to contain all the expired air of the experimental period or so arranged as to measure accurately the volume of expired air and also permit the withdrawal of aliquot samples for analysis. From the CO_2 content of such a sample the total CO_2 output is calculated directly. To determine

the oxygen intake both the oxygen and nitrogen content of a sample must be found (the latter by subtracting CO_2, O_2 and water vapor from the total volume of the sample, the remainder necessarily representing nitrogen). Since nitrogen is neither added to nor subtracted from during the respiratory exchange its total quantity in the expired air equals its total in the air inspired. The volume of the latter (which is atmospheric air) is then computed from its nitrogen content, and the total quantity of oxygen inhaled computed as a known fraction of the inspired air. The oxygen intake of the body is then found by subtracting the oxygen in the expired air from the above quantity.

Since both CO_2 and O_2 are determined volumetrically (by use of the Haldane gas-analysis apparatus or some similar device), the open-circuit type of apparatus is free from the objection mentioned above to which the closed-circuit method is subject. It has the particular advantage of lending itself to outdoor metabolism studies, the expired air being collected into a large rubber bag which the subject carries on his back.

Calculation of Metabolism from Respiratory Data.—Both the closed-circuit and open-circuit methods described above give, in competent hands, accurate data as to the actual amounts of oxygen taken into and carbon dioxide exhaled from the body of the subject during the experimental period. The metabolism must be calculated from these. As already pointed out (page 380), the respiratory change *during any given period* is quantitatively indicative of the metabolism for the same period only provided: (*a*) There is no over-ventilation of the lungs; (*b*) no oxygen deficit is being incurred; (*c*) no previous oxygen deficit is being made good. The accepted experimental conditions (page 456) preclude oxygen deficit as a factor in ordinary basal metabolism determinations. Over-ventilation must be guarded against with care by accustoming the subject to the apparatus and avoiding causes for excitement while determinations are in progress.

Assuming the respiratory exchange to be correctly indicative of the metabolism, the latter can be computed directly from the oxygen consumption, provided the character of the fuel burned is accurately known. Without this knowledge the computation cannot be made except roughly, since the "caloric value" of a liter of oxygen varies between 4.48 and 5.05 Calories, according as fats or carbohydrates predominate in the fuel. The body utilizes a mixture of carbohydrates, fats and deaminized protein residues determined in part by the equilibrium prevailing among the nutrients in the body (page 187), and in part by the relative magnitude of basic and functional metabolism (muscular exercise tends to increase the proportional utilization of carbohydrates; page 88). The clue to

the character of the fuel mixture is obtained from the *respiratory quotient*, *i. e.*, the ratio $\frac{\text{Vol. } CO_2}{\text{Vol. } O_2}$ (page 380), which fact explains why CO_2 determinations as well as O_2 determinations are essential in metabolism studies.

The Respiratory Quotient, an Index to the Character of the Fuel.— When fat alone is being utilized the respiratory quotient (commonly indicated by the symbol R. Q.) is 0.707; when protein alone, 0.801; when carbohydrate alone, 1.000. The mixed fuel characteristic of human metabolism gives an intermediate respiratory quotient, averaging in the neighborhood of 0.82. Since three variables are involved, the exact proportion of proteins, carbohydrates and fats cannot be computed directly from the respiratory quotient, but if one of them is known the other two can be computed. Fortunately the protein factor is easily determined independently, by estimation of the nitrogen content of the urine. Repeated investigation, dating from the work of Voit and Pettenkofer (1866), has demonstrated that the urinary nitrogen times 6.25 gives the weight of protein metabolized during the period covered by the formation of the collected urine (an allowance of 2 per cent is usually made for nitrogen eliminated in the feces).

The usual practice in physiological calorimetry is to express quantities of individual fuels not in terms of weight, but of proportional energy contribution. Thus, instead of saying that 90 mg. of protein are utilized the statement would be that protein contributed 20 per cent (or whatever) of the total energy. The method of determining protein from urinary nitrogen, as described above, gives actual weight. To convert this to proportional energy contribution it is obvious that the total metabolism must be known, and also the "fuel value" of a gram of protein. The fuel values of the different foodstuffs per gram are: Protein, 4.1 Calories; carbohydrate, 4.1 Calories; fat, 9.3 Calories. The total metabolism can be roughly estimated from the total oxygen consumption by adopting tentatively an intermediate caloric value per liter of O_2, 4.75 for example. The proportional contribution of protein is then determined approximately, and since a slight error at this point does not affect the final determinations appreciably, an approximate figure is not objectionable.

Various methods of completing the calculation are available. One of the simplest is by use of a chart worked out by E. F. DuBois (Fig. 50). On the chart a horizontal abscissa is measured off at the level indicated by the protein calorie percentage (at left of figure). Where this abscissa cuts the diagonal for the respiratory quotient (at base of figure) a vertical is erected to the point of

intersection with the line marked "caloric value of oxygen." This point gives the precise value of the latter for the particular fuel mixture being oxidized. Multiplying the "caloric value" by the volume of oxygen gives the total metabolism. To illustrate: A certain subject consumes 17 liters O_2 and exhales 15 liters CO_2 in an hour. His nitrogen elimination during the same period is 0.5 gm. By calculation his respiratory quotient is 0.88 and his protein utilization 3.12 gm., equivalent to 12.8 Calories. Multiplying the oxygen consumption, 17 liters, by the mean caloric value of a liter of the gas, 4.75, we obtain 81 Calories as the approxi-

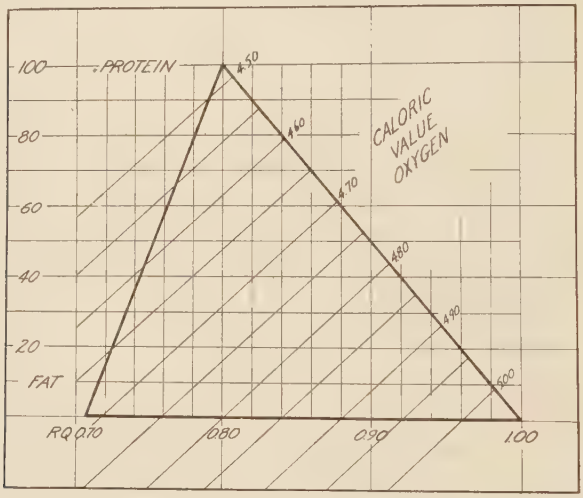

Fig. 50.—Chart for determining caloric value of oxygen. See text for method of using. (E. F. DuBois.)

mate total energy yield. The protein portion, 12.8 Calories, is 16 per cent of this total. Accordingly, the abscissa is laid off at the level 16, and is found to cut the respiratory quotient diagonal corresponding to 0.88 directly below the oxygen caloric value 4.80. This is the value properly to be multiplied by the oxygen consumption, 17 liters, instead of the mean value first used. The actual metabolism is thus found to be 81.6 Calories. The expected metabolism can be computed from the subject's age, weight and height, with the aid of Fig. 49 and the table on page 455. If the two fail to agree within reasonable limits the subject comes under suspicion of suffering from disturbed metabolism.

The distribution of the non-protein fuel between carbohydrate and fat is established by means of another DuBois chart (Fig. 51). The same data as used in the previous calculation are applied. In the position occupied by oxygen caloric values in Fig. 50 this chart

has percentage carbohydrate values. Coördinates are erected as described above. The data cited in the illustration, applied to this chart, show the energy derived from carbohydrate to be 58 per cent of the whole. Adding this to the protein per cent, 19, gives 77 per cent derived from other nutrients than fat. The balance, 23 per cent, must therefore have come from combustion of the latter fuel stuff.

Factors Affecting Basal Metabolism.—Beside the factors of age and sex already mentioned (page 455) various others influence basal metabolism. Food ingestion increases metabolism directly (the so-called "specific dynamic action" of the nutrients). The effect is particularly marked in the case of proteins. When (in dogs) the

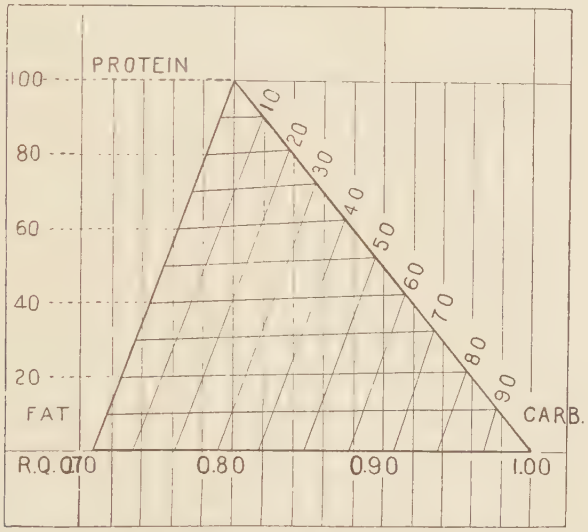

Fig. 51.—Chart for determining distribution of non-protein fuel between fat and carbohydrate. See text for description. (DuBois: Basal Metabolism in Health and Disease.)

total estimated basal requirement was fed in the form of meat the metabolism was increased on the average as much as 36.7 per cent (Rubner). In other words, all the material fed was oxidized and the animals' own tissues to the extent indicated in addition. Other nutrients have less pronounced action. Fat fed, as above, to meet the estimated requirement exactly, raised the metabolism 12.7 per cent; sugar, 5.8 per cent. The calorigenic effect of proteins is attributed (Meyerhof and co-workers) to a specific action of lactic and pyruvic acids, presumed to be formed as a step in the synthesis of carbohydrate from non-nitrogenous protein residues following deaminization (page 182). Hence basal metabolism determina-

tions are made long enough after the ingestion of food to permit nutrient equilibrium to become established, *i. e.*, in the *postabsorptive* period. The calorigenic action of proteins is so pronounced as to be utilized in the dietary treatment of obesity.

Basal metabolism per unit of body surface is reduced somewhat in sleep, presumably on account of the decline in or disappearance of skeletal muscle tonus. In emaciation due to prolonged undernutrition the metabolism also falls off. In a particular investigation (Magnus-Levy) a subject reduced by semistarvation to a weight of 36.2 kg. had a metabolic rate of 26.6 Calories per square meter per hour, as contrasted with 40.5 Calories after the weight had been brought up by liberal feeding to 52.2 kg. This is obviously a conservative reaction. Its mechanism is not understood.

The most striking effects on basal metabolism result from changes in the quantity of hydrogen transporters present in the body. Adrenin is stated (Boothby and Sandiford) to increase the metabolism promptly to the extent of 50 Calories per mg. and thyroxin more gradually, to the extent of 1008 Calories per mg. (page 198). Disturbances in thyroid gland function are attended typically by changes in basal metabolic rate. For example, Boothby and Sandiford report the following findings in a large series of cases: Exophthalmic goiter (chemically altered thyroxin; page 199), basal metabolism more than 20 per cent above normal in 92 per cent of cases, more than 50 per cent above normal in 52 per cent of cases; hyperthyroidism proper (toxic adenoma), metabolism more than 20 per cent above normal in 65 per cent of cases, more than 50 per cent above normal in 13 per cent of cases; hypothyroidism (myxedema), metabolism more than 20 per cent below normal in 82 to 83 per cent of cases.

In fever the basal metabolism is increased on the average about 10 per cent for each degree centigrade of temperature rise above normal (DuBois). The increase is looked on as due directly to the rise in temperature rather than to any specific dynamic action of disease toxins (page 451).

TOTAL METABOLISM.

Basal metabolism as defined includes the entire *basic metabolism* (page 59) together with an unavoidable minimum of functional metabolism (heart-beat, breathing movements, secretory activities of kidneys and other glands) and, in children, the excess energy of growth metabolism (page 62). Even though no unnecessary motions are made, the *total metabolism* for any considerable period necessarily exceeds the basal, because it is bound to include more functional metabolism than the above minimum. Food must be eaten, digested and absorbed, the bladder and colon must be

evacuated. Furthermore the specific dynamic action of the ingested nutrients increases metabolism above the strict "basal" level. Most estimates consider these factors sufficient at their minimum to increase total metabolism by about 10 per cent, raising the total for the twenty-four-hour day from about 1700 Calories to about 1870 Calories. Any energy yield above this latter figure is due predominantly to the functional metabolism of additional muscular exercise.

Muscular exercise of any sort increases total metabolism by an amount determined: (1) By the quantity of work done; (2) by the *efficiency* of the muscles (page 88). If the total metabolism is measured in the usual way, by determinations of the respiratory exchange, the result gives the entire energy yield, which includes three items: (*a*) Basal metabolism itself; (*b*) the mechanical work done by the muscles; (*c*) the additional heat yield due to muscular inefficiency. If the mechanical work is measured directly the efficiency of the body as a whole can be computed, and if the basal metabolism is known the net efficiency of the muscles can be determined.

Some interesting data on the "metabolic cost" of different kinds of work are available. Assuming a basal metabolism of 70 Calories per hour the effort of standing erect involves a total of about 78 Calories (12 per cent increase; Smith). The commonest form of activity in man, horizontal walking, is done most efficiently, *i. e.*, with least waste of energy, at a speed of about 2.8 km. (1.7 miles) per hour, or 100 feet per minute; in other words, at a very leisurely pace. The total metabolism of a 70-kg. man maintaining that pace for one hour is about 170 to 180 Calories (calculated from Smith). At the ordinary walking pace, about double the above, the total is about 315 to 320 Calories. In the extreme muscular exertion of rowing at speed, Y. Henderson and Haggard report the maintenance for six minutes of total metabolism amounting to approximately 30 Calories per minute, or a rate of 1800 per hour (marked oxygen deficit was being incurred, consequently this rate could not be maintained for more than a few minutes). The data of Henderson and Haggard indicate also that a theoretical maximum metabolism of about 19 Calories per minute, or 26,000 per twenty-four-hour day might be sustained indefinitely, were fatigue not to supervene (4 liters O_2 utilized per minute; caloric value, 4.75 Calories per liter). The significance of fatigue as a factor in reducing human working power is clearly brought out by the observation that a total metabolism of as much as 6000 Calories per twenty-four hours implies a hard day's work (Langworthy); Wood and Mansfield report probably the largest sustained metabolism on record, *i. e.*, a daily average of 8083 Calories per man in a group of 50 Maine lumbermen.

DIETARY FUNDAMENTALS.

Requisite Energy.—Whatever metabolism the organism displays must be sustained either by the ingested food or at the expense of stored nutrients (page 188). In the long run the former is the significant source. Clearly from the energy standpoint the first requisite of the diet is that it supply as much energy as the metabolism liberates. This is what happens normally. Indeed, a striking feature of the functioning of the organism as an automatic self-regulatory entity is the accuracy with which in the majority of individuals day by day, under the sole impulsion of hunger and appetite, the food intake balances the metabolic requirement, so that the body neither gains nor loses weight.

Adequate Protein.—A second requisite is that enough protein be ingested to make good protoplasmic wastage (page 60) after providing for the inevitable minimum of deamination of amino-acids (page 182). The former requirement would be met in a person of average size by a daily intake of about 14 gm. were the amino-acid proportions of the ingested proteins the same as of the tissue proteins, and the intake distributed evenly over the twenty-four-hour day, to avoid "flooding" of the liver (page 183). Such deamination as necessarily occurs on an ordinary mixed diet, ingested in three meals, is taken care of, together with protein wastage, by a total daily ingestion of 30 to 35 gm. protein (Chittenden). This minimum is exceeded in practice by virtually the entire human race. The significance of this fact is discussed in a later paragraph.

Avoidance of Ketone-body Excess.—A third requisite is that the proportion of fat in the diet be not so large as to lead to excessive production of ketone bodies. As already noted (page 234), these bodies appear to be formed in the course of conversion of fats to carbohydrates, and if the utilization of fats is on too large a scale will consequently be present in the blood in injurious amounts. Ordinary diets contain so large a proportion of carbohydrates that this scale is not even approached in healthy organisms not forced by starvation to subsist on their own tissues. Carnivorous animals and Eskimos, however, live habitually on diets extremely poor in carbohydrates, and often correspondingly rich in fats. Do they display ketosis in consequence? An all-flesh diet is so deficient in carbodydrate that none is indicated (except in liver) in official analyses of meat,[1] although as a matter of fact, most kinds of lean mean contain about about 1 per cent of their weight of glycogen (page 89) or approximately 0.05 gm. for each gram of protein. In addition to this small carbohydrate fraction, a meat diet yields a glucose-like fraction from the group of amino-acids which yield

[1] Bull. No. 28, Office of Experimental Stations, U. S. Department of Agriculture.

glucose residues on deaminization (page 182), and another from the glycerol of the fat. A group of four amino-acids, leucine, phenylalanine, histidine and tyrosine, yield aceto-acetic acid on deamination, and accordingly act like fatty acids in metabolism.

An investigation of an Eskimo dietary (Krogh) indicates an average daily consumption of 282 gm. protein, 135 gm. fat and 54 gm. carbohydrate, the latter derived mainly from edible portions of seal and whale skins. In this diet protein furnishes nearly as much energy as fat (1150 Calories from protein; 1250 Calories from fat). To design a diet in which fat furnishes most of the energy the proportion of carbohydrate must be considerably increased. In practice a dietary in which fat yields 75 per cent of the energy, protein 10 per cent, and carbohydrate, 15 per cent, is about as rich in fat as can be depended on to show no excess ketone-body formation.

Dietary Accessories.—The fourth and final requisite of an adequate diet is that sufficient amounts of the various salts and vitamins be included. This requisite is met by ingestion of vegetables, fruits and dairy products. Items in the last category have high nutritive value as well, but fruits and vegetables, with few exceptions, are more important as sources of salts and vitamins than as energy providers.

Some investigators have urged the importance of balancing the diet in respect to "acid-forming" and "base-forming" qualities. In general, meats and cereal foods are acid-forming; fruits and vegetables base-forming (tomatoes, cranberries and plums are exceptions). In view of the large continuous production of acids in metabolism and of the ease with which ammonia is synthesized in the kidney (page 148), the value of special efforts to balance the diet of healthy persons in respect to acids and bases is questionable, although in conditions tending toward acidosis (page 167) or alkalosis (page 232) the selection of a balanced diet is obviously advantageous. Furthermore, a less acid urine has higher solvent power for urates than a more acid; consequently a base-forming diet is advantageous in treatment of certain forms of renal calculi.

NITROGEN EQUILIBRIUM.

From the facts of protein metabolism thus far described, it should be clear that protein wear and tear results in a daily loss of nitrogen from the body of not less than 2.2 gm. (corresponding to about 14 gm. protein, the conversion factor being 6.25). If protein of suitable amino-acid composition were ingested to this amount under conditions such that no deaminization were to occur, the wastage would be exactly made good and the intake of nitrogen would just balance the outgo. The body would then be in *nitrogen equilibrium* at the lowest possible level (sufficient ingestion of non-nitrogenous

nutrients to meet all energy requirements is assumed). In practice this theoretical minimum is impossible to attain. Some deaminization is inevitable, hence, if only 14 gm. of protein are ingested a portion is deaminized, yielding a quota of urinary nitrogen to be added to the nitrogen minimum derived from protoplasmic wear and tear; some "stored" protein (page 184) is sacrificed meanwhile to maintain the integrity of the cells. The nitrogen balance is negative, more being eliminated in the urine than is ingested in the food.

The lowest practical level of nitrogen equilibrium in man is attained with a daily ingestion of 30 to 35 gm. protein, or 4.8 to 5.5 gm. nitrogen (page 464). When more than this is consumed the entire surplus undergoes deaminization and the nitrogen split off from the amino-acid radicals appears in the urine; consequently nitrogen equilibrium is maintained at the precise level determined by the protein consumption. The maximum limit is set by the ability of the organism to digest and absorb proteins. A positive nitrogen balance, *i. e.*, intake exceeding elimination, is seen normally only in growing organisms or in adults after a period of deficient nourishment such that "storage" proteins (page 184) suffer depletion. During restoration following such a period, while the storage of proteins is being brought up again to the capacity of the tissues, nitrogen retention occurs. If the depletion has been pronounced, as in a wasting sickness, restoration may occur at a rapid rate. An average gain of 150 gm. protein per week for four weeks is reported in one case (Von Hoesslin).

OPTIMUM PROTEIN CONSUMPTION.

The major portion of the human race ingests daily more than double the quantity of protein indicated above as just sufficient in practice to maintain nitrogen equilibrium. Only two considerable groups among the many thus far studied, *i. e.*, the poor of Southern Italy, and the poor among the Bengalis of Southern India, are reported to subsist regularly on a diet containing less than 60 gm. protein per individual per day. The question at once presents itself whether there is a sound physiological reason for the almost universal excess consumption. Not much direct evidence is available on the point. It is stated (McCay) that the Bengalis on a protein-poor diet have demonstrably less capacity for hard muscular work than related peoples living under similar conditions but eating a diet richer in protein. Furthermore, some of the Italians on low protein were observed to show marked improvement in muscular power when fed a protein-rich diet. The diminished muscular strength may conceivably be related to a narrower margin of "storage" protein when the diet is consistently low in that nutrient.

During the World War serious consequences of undernutrition were seen, but the energy content of the diet was low as well as the protein, consequently ill effects due to insufficient protein could not be altogether separated from those due to inadequate energy. A phenomenon of general occurrence was loss of body substance, accompanied by a negative nitrogen balance, showing depletion of storage proteins. The consequent emaciation resulted, in turn, in diminished basal metabolism (page 462), a fact counted on to some extent by the authorities of blockaded countries in arranging for rationing civilian populations.

Actual dietary studies (compiled by Langworthy) show the average daily protein consumption of various races and occupations to range from a minimum of 86 gm., observed in inmates of institutions, to a maximum of 177 gm., seen in American laborers at very hard work. German laborers (prewar) are credited with 134 gm. One other group observed, 14 in number, consumed on the average more than 118 gm. The grand average for all the groups is about 100 gm. There is no doubt that this level of consumption could be reduced by one-fourth without harm. Whether it might be still further reduced (to about 60 gm.) is a subject of controversy (for details consult Lusk). Since surplus protein is efficiently utilized for energy the question is of only moderate physiological interest.

PRACTICAL DIETARIES.

The choice of foods is dictated mainly by the appetite (page 464) subject to the skill of cooks and marketers and to economic and seasonal factors. Waste in kitchen and at the table and failure to digest operate to reduce the amount actually utilized below the amount consumed by 6 to 10 per cent. Large numbers of dietary studies have been made, covering many parts of the earth and the economic range from extreme poverty to great wealth. Tables of the nutritive values of all the commonly used foodstuffs are also available (see Sherman). One can determine fairly closely, therefore, what quantities and proportions of nutrients are actually consumed by the various classes of the population. Summarized briefly, the main findings applicable to Americans and peoples of similar dietary habits are as follows: The energy quota per healthy adult starts with a minimum of about 2000 Calories for men and 1800 for women leading strictly sedentary lives; the average for city dwellers, both sexes, is about 2500 Calories; manual workers ingest from 3000 Calories upward, according to the severity of their toil; the total energy tends to be distributed in the proportion; proteins, 11 to 18 per cent, fats, 25 to 35 per cent, and carbohydrates sufficient to make up the total of 100 per cent; these limits are maintained over a wide range of economic conditions, except

that poverty cuts down the proportion of fats materially. A rough but useful measure of the energy value of a mixed diet is derived from the fact that a pound as served at the table, yields on the average about 1000 Calories of utilizable energy.[1]

EFFECTS OF UNDERNUTRITION.

During the World War the blockaded nations were forced to a diet in which the calorific allowance per person was materially below the minimum indicated above for persons of strictly sedentary habits. At times the allowance fell as low as 1344 Calories (Rubner), divided as follows: Proteins, 9.5 per cent; fats, about 10 per cent; carbohydrates, about 80.5 per cent. Owing to inequalities of distribution not every one got even this amount. Among the prominent physiological effects were: (*a*) Loss of weight estimated to average 20 per cent in adults; (*b*) marked disinclination to exertion, either physical or mental, so that laborers worked much less efficiently, children ceased to play, mental apathy became pronounced; (*c*) greatly increased susceptibility to fatigue, great weariness or even prostration attending tasks that would ordinarily be accomplished as a matter of routine; (*d*) a marked slowing of the heart and reduction of arterial pressure, correlated with, (*e*), the reduced metabolism per unit of bodily surface mentioned earlier (page 462). Similar symptoms attributable to chronic undernutrition are observable among the very poor in times of peace. It is noteworthy that these effects develop only after the undernutrition has persisted long enough for both the adipose tissues and the "storage" proteins to have become considerably depleted.

Effects of Inanition.—If a human being starves himself completely, except as to water, he at once begans to utilize his "storage" proteins to make good protoplasmic wear and tear, and to draw upon his glycogen, adipose tissue fat and the storage protein to maintain his total metabolism. The rate at which bodily stores are depleted for the latter use depends, obviously, on the amount of the total metabolism. A starving man after becoming emaciated may be expected to lose about 300 gm. of tissue a day (equivalent roughly to 1200 Calories energy), provided muscular exercise is avoided, and may accordingly live for a considerable time before exhausting his utilizable supplies (one of the Irish "hunger strikers" survived more than seventy days). The basal metabolism falls day by day as the mass of muscular tissue shrinks; ketone bodies make their appearance as soon as the main glycogen store is materially reduced (page 234), and continue present thereafter, showing that instead

[1] For further discussion of dietetics see Lusk (Science of Nutrition) or Sherman (Chemistry of Food and Nutrition).

of the fats being exhausted early, before storage proteins begin to be drawn upon, both are utilized simultaneously. Experiments on lower animals show that the greater the amount of fat present to begin with the longer the survival.

The mental apathy so characteristic of chronic undernutrition is not always present in acute starvation until the very end. The indication is that the nervous structures may be maintained practically normal up to the point of exhaustion of stored material. The last stage of starvation is signalized by an increase in basal metabolism, the so-called "premortal rise." This may be interpreted as marking the point at which stored material, both fat and protein, is exhausted. The metabolic processes go on thenceforward at the expense of substances essential to the physico-chemical protoplasmic system. In other words, the machine begins to burn itself up, and in so doing produces heat more rapidly than while intact.

Summary.

The *energy units* used in calorimetry are the gram calorie (microcalorie) and more conveniently the large calorie, one thousand times as great, sometimes distinguished by use of the capital initial letter (Calorie).

In mammals as a class the *basal metabolism* is approximately 40 Calories per square meter of body surface per hour. The correlation with body surface is thought not to be fundamental, but to arise from the fact that body surface is directly proportional to mass of active protoplasm, the latter being the determinative factor in metabolism.

In man the *heat yield per unit of surface* is not a fixed constant, but varies with age and sex. The maximum occurs at about two years of age. Metabolism is somewhat higher per unit of surface in males than in females. A table of average data is given in the text.

Body surface is calculated from weight and height by various formulæ, of which the one of DuBois is in common use. By means of a simple chart the formula can be conveniently applied. The surface of a man of average weight and stature is approximately 1.8 sq. m.

Basal metabolism in an averaged-sized adult male is at the rate of approximately 70 Calories per hour, or 1700 Calories per twenty-four-hour day. The bodily conditions to be realized are non-absorption from the alimentary tract, complete repose in the waking state and comfortable warmth.

Direct calorimetry as applied in physiology consists of measuring the actual heat yield of a living organism in a specially designed

calorimeter. Technical difficulties limit the use of this method as compared with the various indirect methods.

A simple means of estimating the metabolism indirectly is to determine the *energy value* of the *ingested food* and *excreta*, and by difference the energy turnover of the body. This method is applicable only when no change in body weight occurs.

Indirect calorimetry as commonly practised consists of determinations of oxygen consumption and carbon-dioxide output, the fuel consumption and consequently the energy turnover being computed therefrom. The respiratory exchange is quantitatively indicative of the metabolism in the absence of conditions causing oxygen deficit or over-ventilation of the lungs.

For *calculations of total metabolism* the data required are: Oxygen consumption, respiratory quotient and protein consumption; the first and second are derived from the respiratory exchange; the third from estimation of urinary nitrogen. Convenient charts (DuBois) enable the calculations to be made readily.

Basal metabolism is increased by ingestion of foods (*specific dynamic action* of the nutrients); the action is particularly marked with proteins. In *sleep* and in *emaciation* due to undernutrition the heat yield per unit of body surface declines. Changes in *quantity of hydrogen transporters* present in the body are reflected quantitatively by changes in basal metabolism. *Fever* increases metabolism about 10 per cent for each degree Centigrade above normal.

Total metabolism includes at the minimum a certain amount of functional metabolism, associated mainly with food ingestion, and the specific dynamic action of ingested nutrients, in addition to the basal metabolism proper. The increase due to these adds about 10 per cent to the basal metabolism. Further increases are due to muscular activity. Maximum total metabolism at the rate of 30 Calories per minute for a few minutes has been observed. The practical daily maximum, capable of being sustained over a period of days, rarely exceeds 6000 Calories. The human average is nearer 2500 Calories.

In order for the *diet to be adequate* several conditions must be met, of which the first is that the *total energy* of the utilizable food shall balance the energy of metabolism. In the majority of normal organisms a very exact balance is maintained automatically under the guiding stimuli of hunger and appetite.

The ingestion of *protein* must be adequate to make good "wear and tear" (about 14 gm. daily) in addition to providing for inevitable deaminization. The practical minimum is about 30 to 35 gm. The actual intake of most normal human beings exceeds this minimum materially.

To avoid *ketone-body* formation the proportion of fatty-acid-yielding food must not be excessive. A diet as rich in fat as permissible furnishes about 75 per cent of the total energy in that form, 10 per cent as protein and 15 per cent as carbohydrate.

An adequate diet includes sufficient quantities of *salts* and *vitamins*. These are obtained by ingestion of vegetables, fruits and dairy products. The desirability of balancing the diet in respect to acid-forming foods (meats and cereal products) and base-forming foods (fruits and vegetables) is more marked in certain pathological states than in health.

Nitrogen equilibrium is realized whenever the nitrogen intake in the food just balances the elimination of nitrogen in the excreta. The minimum level of equilibrium is attained with an ingestion of about 30 to 35 gm. protein daily. Equilibrium is maintained in normal organisms at higher levels up to a maximum set by the ability of the organism to digest and absorb proteins. A negative nitrogen balance implies either insufficient protein intake to balance wear and tear plus inevitable deaminization or a total metabolism so much in excess of the total energy ingestion that "storage" proteins are depleted to supply energy. A positive nitrogen balance is seen normally only in growing organisms or in adults recovering from depletion of storage protein.

Healthy human beings tend to ingest 100 gm. protein, more or less, daily, an amount well in excess of minimal requirements, and susceptible of being reduced by at least one-fourth without harm. Persons ingesting less than 60 gm. daily appear liable to a decrease in muscular power.

Dietary studies show the average energy quota of the food consumed by various classes of the population to be closely correlated with the level of muscular activity maintained by the group as a whole. City dwellers average about 2500 Calories per individual per day. The energy tends to be distributed among the nutrients as follows: Proteins, 11 to 18 per cent; fats, 25 to 35 per cent, balance, carbohydrates.

Chronic undernutrition results in marked loss of weight, mental and physical apathy, increased susceptibility to fatigue, marked slowing of heart and lowering of arterial pressure (correlated with reduced metabolism per unit of body surface).

In *complete starvation* tissues waste continuously and the basal metabolism declines. The nervous tissues are maintained more or less in their normal state at the expense of less essential tissues. The continued presence of ketone bodies shows the depletion of fats and stored proteins to go hand in hand. The last stage of starvation is marked by a "premortal rise" in metabolism.

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(See also bibliography at end of Chapter XI.)

PART IV.

EXTERNAL ADJUSTMENT.

CHAPTER XXX.

RECEPTORS: CLASSIFICATION; SIGNIFICANCE IN REFLEX; RELATION TO SENSATION.

In the preceding chapters it has been pointed out that the organism maintains for its individual cells a remarkably constant set of conditions. At any instant the dynamic equilibrium of the internal conditions as a whole constitutes an equilibrium with respect only to the external conditions then obtaining. Any external change may ultimately cause an upset of the immediate cell environment unless prevented by some sort of adjustment of the body as a whole or of some of its parts. Any such readjustment was shown to be the result of a chain of events known as a reflex (page 120) in which the external change causes the excitation of a receptor, the disturbance thus provoked is transmitted over specialized conducting tissue consisting of two or more neurons and finally causes a response, usually motor, which effects the readjustment.

In the present section we shall consider in detail the mechanisms of bodily adjustment thus briefly outlined. It has been shown that the general characters of the reflex find their explanation in the simpler known properties of irritability and conductivity (page 105). We shall now show that certain features of the reflex depend upon the characteristics of the receptor.

The Receptor a Necessary Part of the Reflex Arc.—The receptor as the initiating member of the arc occupies a particularly significant position. As has been stated (page 103), the receptive neuron makes connection by means of the recepto-neural junction with the receptor, a structure always physiologically and usually anatomically distinct. The fact that the stimulus first arouses activity in the receptor which in turn communicates this activity to the receptive neuron has such important consequences and is so often overlooked that it must be examined in more detail. A mechanical stimulus applied to a nerve trunk causes excitation. If applied to

the skin it causes a sensation of contact or of pain. It might, therefore, be assumed that these sensations were due to direct excitation of afferent nerve fibers in the skin. Such direct stimulation plainly does occur in "hitting the crazy bone." That this is not normally the case is shown by the fact that while for pressure the energy necessary to stimulate a nerve trunk directly is, according to the most reliable figures, 387 ergs; less than $\frac{1}{6000}$ of this, or 0.06 ergs, will cause a sensation of touch if applied to the skin. Even pain, though a thousand times less sensitive than touch, is excited by less than $\frac{1}{6}$ (60 ergs) of the force necessary for the nerve trunk. A similar relation holds for heat applied directly to the nerve and to the intact skin or for chemical stimuli applied to the nerve and to the olfactory membrane or the taste buds. Other stimuli entirely ineffective for nerve fibers readily act upon the appropriate receptors. Thus light may be thrown directly upon the fibers of the optic nerve without effect (page 631), but applied to the retina the inconceivably small amount of 0.8×10^{-12} ergs of radiant energy will cause a sensation.

That we cannot in every case identify the receptor as an anatomical unit does not affect the conclusiveness of the proof of their existence furnished by the lower threshold of normal stimulation as compared with the stimulation of the afferent dendron. The simplest sensory mechanism that has been identified is undoubtedly the "free" intraepithelial nerve endings for cutaneous pain. It is worthy of note, however, that even these endings show minute terminal expansions often in connection with modified epithelial cells—a visible receptive differentiation.

On the basis of evidence such as we have just cited we may therefore safely assume that *in every normal reflex a receptor, physiologically distinct from the conducting dendron of the receptive neuron, is a necessary part of the reflex arc.* An apparent exception to this is offered by the olfactory apparatus (page 539). Here the hair-bearing, exposed portion is physiologically a receptor and the axon leading to the brain a conductor, although both are comprised within the anatomical boundaries of a single cell. This primitive arrangement involves what is common among the protozoa, a marked specialization along different lines by different parts of the same cell.

Selective Sensitivity.—Since every reflex arc starts with a receptor and an impulse once initiated courses in the simpler reflexes over an inherently determined path to a particular effector, it is clear that the adaptive nature of the result must be determined largely by the receptor. For this its selective action is significant. The skin, for instance, contains several types of receptors equally exposed to external forces. When, however, heat rays from the sun fall upon the skin only one of these types is affected, the warmth

receptors, whereas strong pressure is without effect upon these and stimulates only pain receptors. The resulting reflexes are totally different; heat gives rise to vaso-dilatation, pressure to withdrawal. Each reflex is useful as a response to its customary stimulus only; that in either case a useful reflex occurs is dependent upon the selective sensitivity of these receptors.

The amount of energy necessary for mechanical, electrical, chemical or other stimulation of a nerve fiber are not the same since these stimuli act in different and not equally efficient ways. For a single type of stimulus, however, all nerve fibers are about equally sensitive. This is not true of receptors. If to a group of receptors a stimulus not customary for any is applied, some will fail to respond whereas the majority will be stimulated. Those stimulated will require a rather high and approximately equal intensity. But for its customary stimulus each receptor shows a marked and often extraordinary sensitivity. It is this striking selective sensitivity, so important a factor in adaptative behavior, that requires an explanation.

We must at once admit that our knowledge of the ultimate workings of the stimulus upon the receptor is in all cases too incomplete to permit a satisfactory analysis, but certain factors are known and may be stated briefly. In many receptors the selection depends upon the presence of non-excitable accessory structures. Strictly interpreted, the receptor is the structure in which excitation is first produced, the part in which the stimulus first induces a change in the functional metabolism. In a sense organ, such as the eye, however, we find in addition to the essential receptors, *i. e.*, certain cells of the retina from which the nerve impulses start, a number of accessory parts which modify the light in various purely physical ways without at the same time showing any modification of their own metabolism. In fact, few receptors are directly exposed to the action of the stimulus; even such simple receptors as those of the skin receive heat and pressure only after it has been physically transmitted (and modified) by the superficial layers of the skin, which must in this case, therefore, be considered as accessory structures. Certain of these accessory structures bring about selection by screening the essential receptor from forces other than that for which it is specialized. The retina and the olfactory cells, for example, are protected from mechanical stimuli while open to light and odors respectively. A more important type of accessory structure is that altering the configuration or nature of the stimulating force. The force is delivered to the receptive cells unchanged in character but modified in detail, as by the image-forming structures of the eye which transmit to the retina all the light of various intensities and wave lengths that enter the pupil at any instant, but spatially separated and arranged in the image (page 603), or

the sound-conducting apparatus of the ear which receives air vibrations and delivers them to the cochlea unchanged in form but as water waves of increased vigor and diminished amplitude (page 553).

The accessory structures may, on the other hand, transform an ineffective force into a kind of energy utilizable by the receptor. Gravity, for example, does not directly stimulate any receptor, but through its differential effect on accessory structures of differing specific gravities causes mechanical stimulation of the essential receptors. Thus the otolithic membrane in the ear, which, weighted by the otoconia, is more dense than the endolymph, is assumed to pull upon the hairs of the macula in a different direction for each different position of the head (page 507). It is possible that more such transformations will be found as the intimate action of the stimuli upon the various receptors is studied. (See, for example, von Frey's view of the mechanism of touch receptors, page 524.)

Both of these methods have been used to extend the powers of man's recept rs. The microscope and telescope are but additions to the image-forming accessory apparatus of the eye for the production of desired types of modification of the image which the retina must finally utilize. An example of the second method is furnished by the compass which transforms magnetic energy, which is without influence on any of our receptors, into mechanical movements of the needle thus causing changes in light which may affect the eye. We thus "see" the magnetic lines of force. Selective sensitivity may thus be achieved by the exclusion of undesired stimuli, by the concentration or rearrangement of appropriate stimuli or by the rendering effective of certain useful but ineffective stimuli; by these means, in the words of Sherrington, the threshold of excitability of the reflex arc is lowered for one kind of stimulus and heightened for all others.

CLASSIFICATION OF REACTIONS.

Among animals we find a vast number of readjusting activities to which the general term of *reactions* may be applied. Within this term are embraced many degrees of physiological complexity. The term *reflex* (page 120) is properly restricted to a particular type of reaction involving a synaptic nerve arc and characterized by its relative rapidity, independence of consciousness and volition, and predictibility. Both for the simpler and for the more complex activities, the latter in part compounded of reflexes but sometimes containing elements of a different nature, the general term *reaction* will be employed. If we can group in a significant classification these numerous reactions or the receptors initiating them, it will greatly aid in their discussion. We have insisted that all reactions tend ultimately to maintain or to restore the cell environment; the

group of external activities which we are now considering furnish what may be called the "raw materials" with which the mechanisms discussed in Chapters X, XI, XII, XIII and XIV work. Arranged with reference to the materials and forces involved in the maintenance of the cell environment, the majority of the manifold reactions fall into a few simple classes. We have a group of (*a*) *temperature-regulative reactions*, which in mammals and birds coöperate with the internal mechanism discussed above (page 446) to keep the cell temperature constant. They include vaso- and pilomotor changes in the skin and sweating, which affect the rate of heat loss, and changes in muscular tone or shivering which affect the rate of heat production. Ultimately they lead to the seeking of shelter by the animal.

The chemical raw materials involved in regulating the water content, hydrogen-ion concentration, salts, foods, vitamins and the like of the cell environment are found in the water and food taken by the animal and corresponding to these we have a second group of (*b*) *food-getting reactions*. The outgo of materials involved in the regulation of the chemical features of the cell environment is accomplished by a group of (*c*) *eliminative reactions*, including defecation and micturition. Oxygen is furnished to and carbon dioxide taken from the internal mechanisms regulating the gaseous content of the cell surroundings by the (*d*) *respiratory reactions*.

Injury to the organism which might ultimately cause the breakdown of the entire regulatory mechanism and the death of all the cells is guarded against by a very important group of (*e*) *protective reactions*. They range from the simple withdrawal reflex of the limb to flight in response to painful stimuli and include the scratch reflex, coughing, sneezing and others in response to irritating stimuli. These five minister to the individual; a sixth group of (*f*) *reproductive reactions* insure the perpetuation of the race.

If any one of these groups is critically examined it will be seen to contain one end-reflex to which the others are contributory; thus the swallowing of food is the reflex which consummates a series of activities beginning, let us say, with the sight or smell of prey and including its pursuit and capture, the tearing off and the chewing of the flesh. The final activity, as swallowing in the example, is in the great majority of cases clearly a reflex; to this type Sherrington has applied the term *consummatory* and to the preliminary type, which may be but is often not a reflex, the term *anticipatory* or *precurrent*. He points out that the two types differ markedly in what the psychologist calls "affective tone" (page 493); the consummatory reflex brings a feeling of satisfaction and finality or in other cases ease from pain, while the anticipatory reflexes are neither distinctly pleasant nor unpleasant. They also differ in this that of two reflexes simultaneously initiated the consummatory

is, other things being equal, the one that will be carried out; it is *prepotent*, while the anticipatory reaction is inhibited. Certain of the anticipatory reactions are always linked with a particular consummatory reaction, as chewing with swallowing, but others, as locomotion, may form a preparatory stage to any one of a number of consummatory reactions. An animal may run from the sight of an object associated with pain or toward food or its mate. We may accordingly list several groups of anticipatory reactions which cannot, as in the cases given above, logically be attached to one rather than another of the main consummatory reactions, and which are nevertheless important enough to deserve separate recognition. Of these an important class includes (*g*) the *postural reflexes*. It is a striking fact that all animals maintain throughout life some one of a few characteristic postures, each of which is dependent upon the tone of particular muscles reflexly maintained. If this posture is forcibly changed the change is resisted or the posture restored; an example familiar to all is the prompt "catching oneself" in slipping. Closely related to the postural are the (*h*) *locomotive reactions*, including crawling, swimming, walking, running, flying and the like. Another group, (*i*) *prehensive reactions*, is anticipatory to food-getting and other activities mentioned above, but are of such importance in man, where they form the basis of nearly all our skilled activities, that they clearly deserve separate mention.

In most cases the stimulation of a receptor initiates, in addition to the main reaction, a secondary, or (*j*) *receptive reflex*, which adjusts the accessory mechanism and so insures more effective functioning of the entire receptor. These are involved in giving attention; in the eye, for example, they include pupillary adjustment, accommodation and fixation which causes the image of a "new" object to fall on the most sensitive portion of the retina in its greatest possible clearness—properly focussed and with the correct illumination. To this group belong also the "pricking up" of the ears and the contraction of the tensor tympani muscle (page 553), "sniffing" in the case of smell, "smacking the lips" in taste and others.

Most animals show a group of (*k*) *sound-producing reactions* which in man culminate in speech.

Other groups of activities less readily classified on the above basis and in part outside the scope of this work but yet of great importance in human and animal behavior may be mentioned briefly. The tendency for "activity" shown by the horse that "paws the ground" or the "strong man" who "rejoiceth to run a race," and the converse avoidance of activity by the fatigued or sick individual are extremely important but little understood factors in behavior. Possibly they are referable to shifts in reflex

thresholds or to fluctuations in some form of central inhibition (page 730). The spontaneous and diffuse activity or play of the very young may represent a related phenomenon.

In many of the higher vertebrates the conduct is ordered with regard to other individuals of the same species, whereas most of the above listed activities concern only the individual. These *social reactions* include both the avoidance and the seeking out of their fellows, thus producing the solitary or gregarious habits of different animals. Among the gregarious forms the tendency to play and to follow or to be a leader have been pointed out. These and other similar types of reactions lie at the bottom of the social organization of man, and hence are of prime importance; they have more recently been taken as the basis of *social psychology*.

Some of the above reactions represent native endowment, the complete mechanism for carrying them out being present from birth; others are acquired during the lifetime of the individual. It is often difficult to distinguish in the adult to which of these classes a particular reaction belongs.

CLASSIFICATION OF RECEPTORS.

Assuming the above to be a fairly comprehensive survey of the reactions of animals, arranged chiefly with regard to the end-results, it will be worth while to examine the various groups with reference to the initiating receptors. The activities represent varying degrees of complexity; some are comparatively simple reflexes, others are formed of a series of reflexes, each serving as the stimulus to the next, the *chain reflexes*, for which the feeding of the chick may serve as an example; the sight of a wheat grain is a stimulus to pecking, the contact of the grain with the bill leads to its transfer into the mouth, where its contact with the mucous membrane is a stimulus to swallowing. Other reactions contain elements that would be called voluntary. It will be seen at once that a one-to-one relationship between these reactions and the receptors does not hold; each reaction is not set off by a single receptor, nor does a particular receptor always set off the same reaction. A single stimulus to a single receptor does not usually bring about the contraction of a single muscle, but of a number of muscles organized in a definite fashion to which the term *muscle pattern* has been applied. Even the simple withdrawal reflex to a pin prick, a stimulus which involves at the most but a few receptors, requires the coördinated action of the majority of the muscles of the arm. Further than this the single stimulus may initiate activities in widely separated groups of muscles or may be followed by several more or less distinct reflexes.

On the other hand, a group of stimuli resulting from a particular

situation, a *stimulus pattern*, may converge upon a relatively simple muscular act. Thus, the stimulus pattern represented by the sequence of retinal images resulting from a ball flying toward the eye—but not those resulting from a ball travelling in the opposite direction—leads to a wink, as simple a muscular response as can be realized, possibly a single twitch of a single muscle.

Although the above classification will not serve directly for the receptors, yet it has significant relation to the one that will be used. Most of the activities which we have spoken of as externally directed involve the skeletal or somatic musculature and the receptors that initiate them are also somatic in position; for this reason they have been called *somatic receptors* (*somatoceptors*) in contrast to the *visceral receptors* (*viscероceptors*) initiating the reflexes of the internal viscera. What we know of the visceral receptors has been discussed in previous chapters in connection with the various organs and will not be considered further.

The somatic receptors may be subdivided primarily into two groups. Those that initiate and maintain the postural reactions have for their adequate stimuli changes in the relation of part to part of the body, or of the body as a whole to the earth. Since they are thus stimulated by the self activities of posture and locomotion, Sherrington has called them *proprioceptors*. These include the receptors of muscle sense and the non-acoustic labyrinth. The remainder of the somatic receptors are played upon by external forces and hence are called *exteroceptors*. The exteroceptors may be divided again into two groups based upon their relation to the sources of customary stimuli. Some, as the receptors of the skin, are stimulated by objects in contact with the animal, others as the eye, by objects far removed. This last statement must not be misinterpreted; the actual stimulation occurs in the retina and it is upon the retina that the light acts; however, we naturally, if naïvely, say that we "see" the distant tree, and this view, as we shall discover, is biologically the more significant, although it may seem to misstate physical facts. On this basis we have *contact receptors* and *distance receptors*. Of the contact receptors, those for *pain*, the *nociceptors*, should be mentioned first. They respond to a variety of physical stimuli—heat, cold, pressure, chemicals—all of which have a common significance for the organism—harm. They initiate a single group of reactions—the protective. Two kinds of temperature receptors, *warmth spots* and *cold spots*, in the skin give rise in part to the muscular and vasomotor reflexes involved in the regulation of temperature mentioned in the list of reactions above (page 477) and to sensations of warmth and of cold.

Touch receptors located in the skin respond to slight changes of pressure applied to the skin. They initiate few reflexes but give rise to well-marked sensations of contact (touch) which are import-

ant in space perception. All these contact receptors are closely associated in the skin and it is often convenient to use the regional term *cutaneous receptors*.

The remaining contact receptors—*taste buds* and the *common chemical receptors*—are less clearly entitled to their place among the exteroceptors. By some they have been placed in the visceral group because the reflexes initiated in mammals are largely visceral, secretion of saliva, for example. In some fish and in certain invertebrates, however, these receptors are widely distributed over the body and cause obviously somatic responses, such as snapping and seizing; on this basis they have been here considered exteroceptive. This is one of the many cases where a rigid system of classification cannot represent all the biological truths.

The distance receptors comprise the *olfactory receptor* (for smell), the *ear* (*phonoreceptor*) and the *eye* (*photoreceptor*). The olfactory organ, like that of taste, is a chemoreceptor, but, unlike it, is so sensitive that it can pick up out of the air or water minute traces of substances given off by distant objects. The ear responds to a certain range of mechanical vibrations; the eye to a limited range of electromagnetic vibrations of higher frequencies than those affecting the temperature receptors.

If we now return to compare this classification of receptors with the classification of the reactions given above (page 477), we find that certain classes of one are clearly linked with certain classes of the other. The nociceptors initiate the protective reactions; the proprioceptors, the postural reactions; the temperature receptors, in large measure the temperature-regulative reactions. Certain visceral receptors are closely related to food-getting, respiration and elimination. We have still left unpaired the distance receptors on the one hand and most of the anticipatory reactions on the other. It is strikingly true that the distance receptors are not linked directly with any of the consummatory reactions but initiate now one, now another of the anticipatory reactions. The far-reaching significance of this will be considered in detail in Chapter XXXIX.

THE STIMULUS AND ITS EFFECTS.

It will be necessary to introduce at this point certain general conceptions and definitions required for further consideration of the receptors but which cannot be fully appreciated until we have studied at least some of these organs in detail; it may be found advantageous, therefore, to return to these paragraphs after reading some of the following chapters.

A stimulus has already been defined as any agency evoking a response, and it has been pointed out that it apparently always consists of an increase or decrease in the intensity of some physical

force, the various classes of which have been listed (page 70). The term stimulus is also applied less accurately but more naturally to the object with which the force is associated; the retina is stimulated by an increase or decrease in the radiant energy reaching it but it is commonly said to be stimulated by the printed page which reflects the radiant energy.

A stimulus applied to a receptor may be followed by either one or both of two results; an effector may be thrown into action, for example, a muscle may contract, or there may be an experience to which the term *sensation* is commonly applied. The former is objective; it may be seen and studied by the ordinary methods of science; the latter, though part of the very stuff of life to the person experiencing, can only be inferred by others. With adult human beings capable of giving a verbal account such inferences are reasonably accurate; when applied to infants or animals they become hazardous in the extreme. The study of these experiences thus requires special methods, and this field is by many considered the main concern of the science of psychology. What *consciousness* or *awareness* is and just how it is related to the known physiological processes of nerve conduction and the like we do not, and many believe we cannot, know; without further analysis we will consider the experienced sensation, equally with the reflex movement, one of the results of the impingement of the environment upon the organism. Sensations, although difficult of treatment by the ordinary methods of objective science, are clearly important factors in the behavior of men and animals and as such deserve the careful attention of the physiologist.

ATTRIBUTES OF SENSATIONS.

A sensation possesses certain attributes or characteristics which may be analyzed by introspection; concerning the exact number of these attributes there is not complete agreement, but the following may be taken as a representative list: I, *quality;* II, *duration;* III, *intensity;* IV, *extensity;* to these we may add two others less generally accepted, V, *affective tone* (*feeling tone*) and VI, *clearness.* There are also two other attributes, not of the sensations, but of the perceptions aroused by them; VII, *position in time;* and VIII, *position in space* (*localization*).

These will be discussed in order, but before doing so it will be well to point out the relation of this series of attributes to features of the reflex on the one hand and of the stimulus on the other. Since the mechanisms underlying sensation and reflex action are in large measure common to both, we might well expect to find, as we indeed do, a clear correlation between them. Corresponding to the *quality* of the sensation is the *type of reflex* initiated. Thus, the

cutaneous receptors for pain and cold give sensations differing in quality and reflexes differing in type, pain and withdrawal in the former and cold and vaso-constriction in the latter. Stimuli differing in duration give rise to sensations and reflexes differing in *duration*. The *intensity* of the sensation is paralleled by the *intensity* of the reflex as measured by the force of the muscular contractions produced. The *extensity* of the sensation has no clear correlate on the reflex side, although it shows in both cases interesting relation to intensity which will be pointed out later. The analogue of *affective tone* and *clearness* in the sensation are not easily recognized in the reflex, although both show relationship to the prepotency of some reflexes. On the other hand, the perceptions of *position in time* and *position in space*, although of a more complex nature than the attributes already mentioned, are unmistakably represented on the reflex side. The order of occurrence of the reflexes, as of the sensations, follows that of the different stimuli. The reflex scratch of a spinal frog at irritating filter paper shows as clear adjustment to position in space as do any of our sensations. That such a parallelism should be traceable is not surprising. We have said that the stimulation of a receptor and the consequent afferent impulse lead either to a reflex or to a sensation or to both and, since they share the initial portion of an arc including the receptor with its selective sensitivity, they might well show parallelism of response.

Some reflection of these characteristics might also be expected in the initiating stimuli, and it is true that in some cases they may clearly be traced. Thus the intensity of the sensation and of the reflex is found to vary with the intensity of the stimulus. For quality, however, the relation is less simple. In general, different kinds of physical forces as, for example, radiant energy and sound, lead to different sensations or reflexes. But chemical stimuli lead to sensations of both smell and taste or the corresponding reflexes, and within taste the chemical stimulation of sugar gives a sensation of sweet and a reflex of licking or sucking in many mammals, whereas quinine gives bitter and a rejection of the food. On the other hand, the sensation of pain and the withdrawal reflex are initiated by a variety of stimuli, including pressure, extremes of heat and cold, chemicals and the like. Thus, one physiological and one psychological result may come from a variety of physical forces or one type of force may give rise to more than one physiological or psychological result.

The key to this situation lies in the receptor. The majority of the receptors show specific sensitivity and hence each sets in progress a particular physiological or psychological activity when affected by its normal stimulating force. In contrast, the pain receptors show little selective sensitivity but an approximately

equal and relatively high threshold for a variety of stimuli and so come to respond to a group having slight physical relationship but a distinct biological significance—the presage of harm carried by forces so intense as cause injury.

Since not only the nature but also the physiological state of the receptor as well as the nature of the stimulus are factors in determining the response, we must guard against too close an identification of features of the stimulus with attributes of the sensation or characteristics of the reflex—in this way lies confusion. This point will have to be discussed in connection with each of the receptors; here we can only point out an example from the eye. Hue varies with the wave length of the stimulus and brilliance with the intensity; this is generally recognized but the less commonly emphasized fact must be noted, that brilliance also varies with the wave length and hue with the intensity and that both are profoundly affected by the previous stimulation of the part of the retina in question and by the simultaneous stimulation of other parts of the retina (page 647).

Quality.—Differences in the quality or nature of the sensations have long been recognized, as is evidenced by the names which the more outstanding forms have received—sight, hearing, smell, taste and the like. Upon what physiological differences do these differences of quality rest? In ignorance of the relation of sensations to physiological processes no satisfactory answer can be given, but certain of the conditions are known. These were clearly formulated by Johannes Müller in his doctrine of the *specific energy of nerves* (or *specific irritability of nerves*) as early as 1840, and these terms, although hardly such as would be selected in this day, are still used. The significant points are these. The quality of the sensation does not depend upon the nature of the stimulus, since unusual stimuli evoke the same quality as do the usual. Thus the normal stimulus for the eye is radiant energy, but when mechanically stimulated by the finger tip the sensation is also that of light. It does not depend upon the receptor, since the stimulation of the receptive neuron produces the same sensation; the classic example is the sensation of taste caused by the stimulation of the chordi tympani in the middle ear. All qualities are experienced in the apparent absence of external stimuli in the case of dreams and hallucinations. It is, therefore, assumed that the quality of the sensation is dependent upon the particular portion of the brain aroused and that the receptors of the different senses differ in their central connections. This is, indeed, known to be true in most of the cases.

Qualitative differences are not, however, all of the same degree. The sensations from the skin have so great a similarity and are so regularly called up together that they were long included under one sense—"touch"—and, in fact, can only be separately experienced

by the use of special methods of stimulation (page 511). In contrast, sight and hearing are not only distinct beyond the possibility of confusion, but each shows within itself qualitative differences of hue or pitch. Helmholtz recognized two grades of qualitative difference, applying the terms *modality* and *quality*. Differences of *modality* he considered as fundamental and unmistakable differences of sensation; between modalities there are no transitions and even a simple comparison of intensity is not possible we cannot say, for example, whether the brightness of a certain light is more or less intense than the sweetness of a certain solution of sugar, Differences of *quality* are lesser degrees of difference comprised within a single modality; between qualities transitions and fusions are possible and comparisons of intensity can be made. Thus we may pass from red to blue through orange, yellow and green without a sharp change of character and may compare the brilliance of these different hues with consistent results.

But difficulties still remain. The differences between the sensations aroused by different receptors in some cases conform to this definition of modality and enable us to speak of *modal senses*, as, for example, smell and hearing; in other cases physiologically distinct mechanisms give sensations which are commonly confused, as are smell and taste. Although taste may be isolated from smell by so simple an experiment as "holding the nose," most people do not recognize in the "flavor" of an apple or of coffee two modalities of sensation. Again, among the cutaneous receptors cold and warmth, although dependent upon two mechanisms, are usually thought of as forming a single series, and under certain conditions may be so intimately fused as to be indistinguishable (page 517). On the other hand, although taste is looked upon by most as a modal sense, certain workers regard the differences between sweet, salt and the other qualities of taste as modal (page 538).

It is also necessary to consider another probably qualitative difference upon which *localization* depends. Although localization is a perception (page 494) requiring for its development experience, some sort of qualitative difference must attach to sensations from different part of the skin, for example, in order that such a development be possible; this difference is called *local sign*.

In view of the varying degrees of qualitative difference seen in the sensations, it is interesting to note that the receptive mechanisms differ widely in the degree of isolation, both of their receptors and of their cortical areas (page 710). Sight and hearing, which are uniquely different in quality both from each other and the remaining senses, have spatially separated receptors not necessarily affected by the same stimulus and cortical areas distinct in position and definite in extent. On the other hand, the cutaneous receptors touch, cold, warmth and pain—are so intermingled that stimuli applied to

the skin affect two, three or all of them at once, and their cortical areas are so intimately associated in the "body sense area" that no separation has yet been established (page 711). Further, the visual area (page 711) shows within itself differentiation, for example, lesions in the upper portion cause blindness in the upper part of the retina. That is, the quality of local sign has spatial representation in the cortex.

It seems probable, therefore, that the physiological distinctness of the afferent arc corresponds to the distinctness of the quality of the sensation and to the nature of the reflex, and that these differences are not adequately represented by the two degrees of modality and quality, but form a graduated series.

The Intensity and Duration of a Sensation do not Correspond to those of a Constant Stimulating Force.—Before taking up duration and intensity as properties of sensation, it will be advantageous to point out their relation to the essential nature of the stimulus. If a force of constant physical intensity is applied to a receptor neither the intensity nor the duration of this force correspond closely to the intensity or the duration of the resulting sensation. If, for example, we go into a room containing a definite concentration of some odorous substance our olfactory sensation has at first its maximum intensity, from which it declines steadily, until in three or four minutes, depending on the nature and concentration of the odor, it has completely disappeared. In different tests the initial intensity of the sensation corresponds to the concentration of the odor, being more intense for the higher concentrations, but within a particular experiment we have a constant intensity of the chemical excitant related to a sensation continually decreasing to final extinction. Obviously the duration of the sensation does not correspond to the duration of the exciting odor, since, whereas its inception follows that of the stimulus by a short and relative uniformly latent period, its end is influenced by the removal of the odor only if this occurs before the normal decay of the sensation.

This progressive diminution and final cessation of sensation under a constant stimulating force has sometimes been described as fatigue, sometimes as adaptation, but since it may not always have the same cause it seems best to use the term *minuthesis*, which is devoid of implications. We have chosen our example from smell; the same results may be observed in stimulating the skin with objects warmer or cooler than the body (page 515). In a similar manner the constant pressure of glasses or of clothes soon fails to cause a sensation, although a slight change is vividly noticed. An essentially similar but less simple situation may be observed in the retina exposed to a constant light, as we shall see in considering the eye (page 637). In fact, minuthesis is common to the majority of the receptors.

Fatigue.—Fatigue is a well-understood phenomenon in muscle. If the products of metabolism are formed more rapidly than they can be removed and so accumulate, contraction is hindered and finally becomes impossible (page 90). Does the same situation occur in minuthesis? Does the receptor show functional metabolism, and under a constant force do the products of such metabolism accumulate until function is reduced or impossible?

Since, as we have said (page 473), the amount of energy required to stimulate a receptor is far less than that required to stimulate the connected nerve fiber, and since the functioning of the receptors is closely dependent upon a supply of oxygen, we may conclude that they show functional metabolism, liberating more energy than is applied to them in stimulation. The absolute metabolism of the receptors is, indeed, very small, but so, too, is their bulk; the metabolism might be intense and still difficult to measure. Their minute bulk also would favor a rapid recovery.

Some receptors apparently show a true fatigue. Warmth and cold spots individually stimulated soon fail to respond; a behavior agreeing with the criterion of fatigue in muscle. The ear exposed to a continuous sound shows a minuthesis which seldom reaches complete extinction of sensation. If after the minuthesis has developed the sound is interrupted for a short time it is better heard upon its resumption, indicating that fatigue has occurred and that the short rest has increased the ear's power of response.

But neither of these cases conform to the condition of fatigue from a constant stimulating force. The fatigue of a warmth or cold spot is best obtained by touching it several times in succession with a warm or cool rod. If the temperature is kept at a constant intensity by placing the hand in warm or cold water until the sensation has vanished, the temperature receptors will be found capable of further response, giving sensations for a change of approximately 0.5°, as in the beginning. Although the receptors may be inactive, they are not incapable of function. The case of the ear seems to fulfill the condition more adequately since the fatigue is from a continuous sound. Nevertheless a sound is by no means a constant force as pressure or temperature may be. The vibrations of the air are transmitted to the ear and ultimately cause a series of pressure variations on the essential receptors (page 553). For most receptors the effect of a constant force is like that just described for temperature. Although fatigue may occur, the minuthesis under a constant force is not the result of fatigue, as is shown by their capacity of response to a further change. We may cite smell, taste, touch, cutaneous pain, temperature and vision.

Stimuli are Changes in the Intensity of Physical Forces.—What, then, is the cause of the diminution of sensation? This question depends upon a careful consideration of what constitutes a stimulus. If we define a stimulus as an agency evoking a response it is clear

that heat, pressure, light and other physical forces are not in themselves stimuli, since their mere presence will not necessarily cause a response. In fact the forces capable of stimulating are nearly always acting and can be excluded from the receptors only with difficulty. At the moment that a "stimulus" is applied it will be found that some intensity of the force is already acting, even though no sensation is being experienced. Completely "odorless" air is difficult to obtain. Really "sound-proof" rooms are surprisingly difficult to construct. The skin before we touch it with the warmed metal rod is far removed from the absolute zero representing complete absence of heat. The eye presents a more complex situation, but even it is already exposed to light, which even the closing of the lids does not wholly exclude, when the light of a "stimulus" falls upon it. Although it is difficult to exclude the forces which normally stimulate, it is not difficult to find for many receptors a time when the sensation, under an unfluctuating stimulus, has entirely vanished. It is from this zero position of inactivity of the receptor under the application of a constant force that we must start when we stimulate under the most carefully controlled conditions, ordinarily the stimulus cuts in on an existing sensation.

What we actually do when we stimulate is to increase or decrease the force in question at or above a minimum effective rate. If we change the intensity slowly from the initial level we may reach a second and very different level without having stimulated the receptor. If we repeat the same change more abruptly a sensation will result. This is well illustrated by the electric stimulation of the nerve. If a constant current is sent through electrodes resting upon a nerve the attached muscle contracts when the key is closed and when it is opened, but not while the current is flowing. If while the current is flowing it is suddenly increased or decreased the muscle also contracts. If the current is slowly altered by a gradual change of resistance, currents much larger than those effective when opening or closing the key fail to cause a stimulation. More careful testing will show that the change must equal or exceed a certain minimum rate to be effective. This situation may be exactly paralleled on the sensory side by the application, for example, of heat to the skin.

We may then conclude that *the increase or decrease in intensity of an appropriate force equaling or exceeding a certain minimum rate constitutes a stimulus.* An apparent exception may be thought to occur when instead of the intensity the quality of the force varies, as when the wave length of light is altered. However, no change of wave length can occur without a change in intensity; what happens is a decrease in the intensity of one wave length and an increase in the intensity of a second. This view is in harmony with the statement made in discussing stimulation (page 70) that changes in the intensity of forces stimulate by upsetting existing equilibria.

Does either the decrease or the increase of a force, if rapid enough, always cause a sensation? If so, are one or two receptors involved? In the case of touch, either a slight "push" or a "pull" is effective, both apparently through action on the same organ. With heat either an increase or a decrease is felt; it is well known that two distinct types of receptors are present in the skin, one giving sensations of warmth and the other of cold. In smell an increase in the concentration of an odorous substance causes a sensation, but as far as is known a decrease does not. The sensation of thirst apparently is due to a decrease in the water content of certain cells in the throat. Thus all possible combinations are realized.

Duration.—With this conception of the stimulus before us, let us consider duration. Duration is an attribute of all sensations, since we recognize the continuance as compared with the cessation, or are able to say that one sensation is longer or shorter than another. Unless there is a marked change in the cortical condition, such as a shift of attention, the duration of the sensation corresponds to the duration of the activity of the receptor. The onset of the stimulus, or change of force at an effective rate, is followed by the sensation after a lag or latent period, which varies with different receptors but usually does not exceed a fraction of a second. While the stimulus continues (that is, while the intensity change continues) stimulation will recur as frequently as the refractory period of the receptor or receptive neuron will permit, thus producing a train of nerve impulses. If the intensity of the stimulating force is altered to, and maintained at, a new level the duration of the stimulus will be that of the change, the duration of the activity of the receptor and hence of the sensation would correspond to the time required to reach a new physical or chemical equilibrium; during this time the receptor would continue to send out a train of impulses conditioned by the refractory period. For example, we may assume that in smell the entry of some diffusible substance from the air in the nasal cavity into the olfactory cells at a certain rate is a stimulus. If such substance is introduced into the air the sensation will continue until the difference of concentration within and without the olfactory cells has become so slight that the diffusion falls below the critical velocity. If this concentration within the nasal cavity is longer maintained it is without effect; if the concentration in the nasal cavity is lowered before the rate of diffusion has ceased to be effective the sensation is, of course, stopped.

For some receptors, although not for the olfactory, a decrease of the intensity to the initial level constitutes a new stimulus. Where this is true the question of duration is still further complicated; we have one stimulus marking the beginning and another the end of the application of the force. In some cases these stimuli supplement and in others they apparently interfere with each other.

The best known example of such interference is that studied by Keith Lucas in the electrical stimulation of the nerve. It had long been known that when a nerve was stimulated by a constant current the shorter the duration of the current the greater must be its intensity. This had been interpreted to mean that a constant "quantity" of electricity was necessary to stimulate; if the time was short the intensity must be correspondingly increased. Lucas showed that the same relation obtained between time and intensity when the "stimulus" consisted of a short interruption of the flow of a constant current and consequently it was impossible to speak of a "quantity" of electricity. Two stimulations occurred, certain features of which were opposed; if the second followed too close upon the heels of the first it was in part neutralized by the effects of its predecessor and must be more intense to set up a propagated disturbance. It is probable that a similar situation occurs in the stimulation of certain of the receptors; there are indications that it is true of the retina. If the two stimuli, represented by the beginning and end of the application of the force, are far enough separated to prevent interference the sensation arising from the second is often called an *after-sensation* (*after-image* of vision, page 645) on the assumption that it is without external cause, although it results from a stimulus as real and effective as the increase that caused the primary sensation.

Intensity.—Intensity is one of the most obvious and one of the few quantitative attributes of sensation. If a series of stimuli graded in intensity is applied to a sense organ the weakest cause no sensation; with increase a just perceptible strength called the *threshold stimulus*, or *limen*, is reached. Due doubtless to fluctuations in the state of the receptor or the conditions within the central nervous system this is not a fixed intensity. Certain weak stimuli never cause sensation, others distinctly stronger always cause them and between these the stimuli of the intermediate portion of the series sometimes cause and sometimes fail to cause sensations, the proportion of effective stimuli naturally increasing as the intensity increases. The actual threshold must, therefore, be calculated from a number of observations in this doubtful region; it is customary to take a point in the series where half of the stimuli are effective. Stimuli less intense than this are said to be *below the threshold* or *subliminal*.

Above the threshold a series of graded stimuli increasing in intensity produce a series of graded sensations also increasing in intensity. The relation between these two series has been the subject of much study. We have no numerical measure of the intensity of sensation and most psychologists agree that it is not measurable in the sense that the physical stimulus causing it is measurable. The intensity of two sensations resulting from two slightly differing

stimuli may, however, be compared. By a statistical treatment of many such reports a *difference threshold* or *difference limen* may be obtained, corresponding to a just perceptible change in the stimulus. If many difference thresholds are determined in different parts of the range in which the receptor may function it will be found that, for the intensities usually encountered, *the ratio of the just perceptible difference to the strength of the stimulus is approximately constant;* this relation established by Weber, in 1846, for touch is known as *Weber's law*. For the extremes of intensity discrimination is less keen. For an example, see the discussion of discrimination of intensity of light (page 648).

It has already been pointed out that if a force of constant intensity acts upon a receptor for some time the intensity of the resulting sensation steadily falls off. The sensations from a receptor fatigued by continued stimulation also becomes less.

Upon what physiological differences do differences in the intensity of sensations depend? From analogy with muscle, in which we know the mechanism by which the graded intensities of contraction are produced, we might expect intensity to depend upon the number of afferent fibers stimulated. Another possibility is that intensity corresponds to the rate at which trains of impulses are being sent over a given number of afferent neurons. In treating extent the question of intensity will again appear. Data on this interesting subject are meager, and may best be presented in connection with the individual receptors.

Adaptation.—Having shown that in many cases the failure of response in minuthesis is not due to fatigue but to the absence of a true stimulus, and having traced the effects of this conception of the stimulus upon the idea of duration and of intensity, we are in a position to consider more satisfactorily the nature of that form of minuthesis which is not fatigue. The term *adaptation*, long generally used in vision, though less commonly for the other receptors, is the most appropriate. Unfortunately it has also been used in a different sense, that of the general advantageous relation of an organism to its environment—confusion from this source should be guarded against.

For the eye adaptation is usually defined as the process by which the sensitivity is increased when exposed to a weak light or decreased when exposed to a strong light. In accordance with the views outlined above, this definition may be altered to the following form. *A receptor when it ceases to respond to a particular constant intensity of a stimulating force, although retaining its power of response, is said to be adapted to that intensity. Adaptation is the process of shifting the indifferent point of a receptor toward or to the intensity level of the force then acting, or the state of the receptor when such a shift of equilibrium has occurred.* Some receptors seldom reach complete adapta-

tion or are so delicate that complete adaptation is difficult to demonstrate; such will show a greatly reduced response to the acting force.

An adapted receptor is thus fitted to record changes from an indifferent point which is dependent upon the prevailing conditions. The situation strikingly recalls an essentially similar device, the Beckmann thermometer, used for the exact measurement of small changes of temperature about an arbitrarily selected level which this thermometer indicates only approximately. When it is recalled that constant forces are the exception in the life of all animals, whereas fluctuations of temperature, light, odorous substances and other forces in the environment are constantly occurring and that to these the animal must adjust itself, the great value of the capacity for adaptation of the receptors is apparent.

The conception of changed sensitivity as a feature of adaptation is misleading if not incorrect. With the adaptation of the skin to different temperatures there is no marked increase or decrease of sensitivity, merely a shifting of the reference zero to various levels. The eye may be adapted to intensities covering an enormous range, surpassing in this respect all other receptors. Although responding to smaller absolute amounts of light when adapted to low intensities, the eye requires the same proportional change of intensity throughout the greater part of its working range; that is, in relation to the existing light the sensitivity remains constant (compare Weber's law above and see adaptation of eye, page 637).

Extensity.—The sensations from many but not all receptors show *extensity* as an attribute. It is particularly well marked in the cutaneous senses and in vision, but is apparently absent from smell. It is intimately connected with intensity and on the other hand must be distinguished from spatial perception to which it contributes. It carries no position in space but only magnitude; one contact with the skin feels larger than another or one object seen appears larger than another. Since both the skin and the retina present fields containing many similar receptors, it is clear that at least in these cases the extensity is correlated with the area stimulated and hence the number of afferent neurons excited. In general, this corresponds to the size of the physical stimulus, particularly if this is large. With small areas, however, a spreading of the stimulus occurs. Thus a pin-head pressed upon the skin causes a depression, the area of which increases with the pressure, or the image of a small spot of light on the retina spreads by irradiation, affecting a larger area when the light is intense.

For certain conditions, therefore, the extensity and the intensity of a sensation are so intimately related that it is difficult to distinguish between them. For example, the fixed stars, which are geometrical points showing no magnitude through the telescope, give rise on the retina to images which are larger the brighter the star. For

us, then, the brighter star has also the greater extent. On the other hand, in dipping the arm in warm water the intensity of the sensation increases with the area of the skin immersed.

Further data will be presented in treating the individual receptors.

Threshold.—We have spoken of the threshold in connection with intensity; it may be well to note certain additional features now that we have considered the other attributes of sensation. If we vary the intensity of a stimulus we obtain a threshold or just perceptible intensity and a series of difference thresholds or just perceptible changes—these we have noted—and finally reach an upper limit beyond which further increase of intensity causes discomfort, protective reflexes and possible injury. This upper limit of tolerance presents a condition physiologically so distinct that nothing but confusion can come from calling it also a "threshold;" if the figure is carried out it should be called a "lintel" value. The term "threshold" has also been used in connection with quality, extensity and duration in addition to intensity. All these conditions must be specified in order that experimental work may have significance and be reproducible. Since, however, the threshold is a value determined from quantitative features of the stimulus, it seems best to limit the term if not to intensity at least to quantitative aspects of the stimulus and exclude quality. If we consider sound, for instance, we find for each frequency an intensity threshold which rises as we pass from the more usual rates to either more or less rapid ones, until upper and lower limits are reached, beyond which unpleasant effects appear as soon as the increasing threshold intensities are applied, a warning that the physiological range of the ear is being exceeded (page 555). The upper limit of tolerance here comes so close to the threshold that no functional range of intensity exists; to apply the term "threshold of pitch" to any feature of this situation will confuse the picture.

It must be remembered that for the receptors of the skin or retina not only the intensity but also the area and duration of the stimulus are factors which must be known in experimental work, but we should be careful to keep all of these in their proper relation in the conception of physiological stimulation sketched above.

Affective Tone.—Not all psychologists look upon *affective tone* or *feeling tone* as an attribute of sensations, but since the stimulation of a receptor leads somehow not only to a sensation but also in the majority of cases to a feeling of pleasantness or unpleasantness intimately associated with the sensation, we may provisionally so consider it. Its importance for the survival of organisms cannot be overestimated; we have only to imagine how long any group of animals would persist were the unpleasantness of the sensations accompanying protective reflexes to vanish, that is, if pain were abolished.

Clearness.—Many psychologists consider *clearness* to be an attribute of sensations. Every one has had the experience of listening to some faint continuous sound, such as the ticking of a clock and noting that at times it is very clear and vivid while at others it may be very vague or escape consciousness altogether. Since neither the stimulus nor the receptor may have changed, the difference appears to lie within the central nervous system, and we say that our "attention" has altered. New or intense stimuli tend to obtain for their sensations a higher degree of clearness in the same way as their reflexes tend to be carried out in preference to others.

Thus the conditions leading to dominant sensations characterized by clearness, affective tone and persistance in memory seem to be those also leading to dominant or prepotent reflexes.

Position in Time.—Although duration or the degree of continuance as opposed to cessation is an attribute of the sensation, *position in time* requiring comparison with other sensations is obviously a *perception*. It is common experience that our manifold sensations show such an orderly sequence in time; beyond calling attention to this feature of sensation, no treatment will here be attempted.

Position in Space.—*Position in space* or *localization* is a percept both important and involved but which can only be mentioned here. Certain additional features will be presented when the various receptors are discussed. We tend to refer each sensation to a stimulating object and to assign to this object a position in relation to ourselves. But the clearness and accuracy of this reference and its method of development are not the same for all receptors. For certain sensations as hunger this reference is vague, the "pangs" are merely felt to be "within" and are connected with the stomach chiefly because this is one of the organs that we verbally associate with hunger. Other sensations, as those from the eye, are referred to their source with exquisite accuracy.

The basis of space perception is complex; at least three types may be recognized. Most important and fundamental is: (*a*) That peculiar to the muscle sense by which motion is directly perceived, and from which, therefore, a system of relative positions may be developed (page 502). A second type is (*b*) that found in the skin or eye in which a number of similar receptors distributed over a surface permit localized stimulation. To the sensation from each part attaches a characteristic quality or *local sign* already mentioned (page 485), making it possible by experience, particularly in connection with the muscle sense, to develop the capacity of assigning to each stimulating object a position. A third type is (*c*), that represented in man by hearing (page 562) and in some fish by smell (page 543). Here the relative stimulation, either in intensity or time, of two symmetrically placed receptors is affected

by the position of a single stimulating object, thus furnishing a basis for the development of spatial reference.

In the skin and particularly the eye, where both extensity and local sign contribute to the development of space perception, we have the more complex forms of perception of *size* or magnitude in which the parts have differing spatial positions and *form* as in the recognition of letters.

Summary.

A *receptor physiologically* and usually *anatomically distinct* from the afferent neuron is a necessary part of each normal reflex arc.

Upon the *selective sensitivity* of the receptors depends the appropriateness of the initiated reflex action. Selective sensitivity is in part made possible by the accessory mechanisms which may exclude inappropriate stimuli, concentrate or reorder customary stimuli, or transform ineffective stimuli into usable types.

A classification of the types of reactions arranged chiefly with reference to the materials and forces necessary in the maintenance of the cell environment is as follows:

A. Consummatory or prepotent reactions.
- (*a*) Temperature-regulative reactions.
- (*b*) Food-getting reactions.
- (*c*) Eliminative reactions.
- (*d*) Respiratory reactions. These four minister to the maintenance of the physical and chemical features of the cell environment.
- (*e*) Protective reactions. This group insures the integrity of the organism.
- (*f*) Reproductive reactions. This group insures perpetuation of the species.

B. Anticipatory, or precurrent reactions.
- (*g*) Postural reactions.
- (*h*) Locomotive reactions.
- (*i*) Prehensive reactions.
- (*j*) Receptive reactions.
- (*k*) Sound-producing reactions.

Other reactions important but less easily classified include the tendencies for activity and for rest and the social reactions.

A classification of the receptors on the physiological basis of the nature of the initiated reaction is as follows:

A. Viscероceptors (not treated in this section).

B. Somatoceptors.
- (*a*) Proprioceptors.
  - Muscle sense (motoceptors).
  - Non-acoustic labyrinths.

(*b*) Exteroceptors.
- Contact receptors.
  - Cutaneous pain receptors (nociceptors).
  - Cold receptors, Warmth receptors } Temperature receptors.
  - Touch receptors.
  - Common chemical receptors.
  - Taste receptors.
- Distance receptors.
  - Olfactory receptors.
  - Auditory receptors (ears).
  - Visual receptors (eyes).

A comparison of these two classifications shows that: Cutaneous pain receptors initiate protective reactions, propriceptors initiate postural reflexes, temperature receptors initiate most temperature-regulative reactions, viscероceptors initiate most food-getting, respiratory and eliminative reactions.

The distance receptors are not directly connected with any of the consummatory reactions, but serve now one, now another of the anticipatory reactions.

The mechanism of selective sensitivity insures that a receptor normally responds to one type of force only. *An increase or decrease in the intensity of such a force exceeding a certain minimum rate constitutes a stimulus.* The application of a stimulus to a receptor may cause either a *reflex* or a *sensation* or both.

The *attributes* of sensations are:

I. Quality.
II. Duration.
III. Intensity.
IV. Extensity.
V. Affective tone (feeling tone), VI. Clearness } Less generally accepted.

The attributes of the perceptions aroused are:

VII. Position in time.
VIII. Position in space (localization).

There is a clear correlation between these attributes and the characteristics of the reflexes initiated by the same receptors.

The *quality* of the sensation is dependent upon the particular *portion of the brain aroused*, and the different senses differ in their central connections. The receptors vary widely in the degrees of qualitative difference which they show.

Minuthesis is the diminution in intensity of the sensation aroused by a receptor subjected to a continuous intensity of a stimulating force. Fatigue of a receptor, as of other structures, for example, muscle, *is the diminished power of response due to failure of the restorative processes to keep pace with the functional metabolism.*

A receptor when it ceases to respond to a particular constant intensity of a stimulating force, although retaining its power of response, is said to be adapted to that intensity. Adaptation is the process of shifting the indifferent point of a receptor toward or to the intensity level of the force then acting, or the state of the receptor when such a shift of equilibrium has occurred.

With stimuli of graded intensities we may determine a *threshold* or *just perceptible intensity* and a series of *difference thresholds* representing just perceptible changes in any part of the receptive range. These latter are found to bear an approximately constant ratio to the level of intensity at which they are determined; this relationship is known as *Weber's law.*

Position and movement in time and *in space* are percepts varying in vividness and accuracy and in method of development in the various receptors.

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CHAPTER XXXI.

THE PROPRIOCEPTORS.

Maintenance of Posture.—All animals when at rest under normal conditions preserve an habitual and characteristic posture varying with the species. With a few minor exceptions this is an active process by which a position unstable with respect to gravity is maintained by continually varying degrees of contraction in large groups of muscles. We stand not by virtue of stiff legs far apart as does a table, but like the juggler's pole by the constant restoration of a position from which we are ever falling. If the vigilance of the nervous system slackens or fails, as from the slowing of the cerebral circulation or the concussion of a blow on the jaw, we collapse into a mere mass of flesh and bone; indeed, by how perilous a juggling feat we maintain our erect position is seen from the statistics of violent death in which death by falling represents the largest single item, including about one-sixth of the total number of fatalities.

Restoration of Posture.—Not only is the posture of any animal the result of constant activity, but any attempt to alter the posture by force meets with active opposition or, if temporarily successful, is followed by active restoration of the former posture. Thus if we attempt to extend the flexed hind leg of a frog we meet with resistance and considerable force must be applied; if we release the extended leg it is at once replaced in the normal position. The same is true of the folded wing of a pigeon. If a cat or dog is pushed from the standing position, or if the support on which it stands is tilted, there is an immediate reaction of restitution or righting reflex.

Habitual Posture a Position of Readiness for Locomotion.—The assumption, maintenance and restoration of position, accomplished by the postural reflexes, insures a state of readiness for other activities. The usual type of somatic response involves the stimulation of some exteroceptor and a resulting movement of the animal which may vary from the flicking of an eyelid to running in which nearly every skeletal muscle is violently active. Most of these activities, but particularly locomotion involve changes of posture, and it will be noted that the habitual postures of most animals are adapted to their modes of locomotion; in the frog at rest the flexion of the hind legs keeps it in readiness for a leap; in the bird the posture of perching is one from which it may instantly launch into flight.

Since it is only upon the background of appropriate posture that effective activity of the muscles of locomotion is possible, we must first consider the postural reflexes and the receptors that initiate them.

Guidance of Locomotion and Other Activities.—But the functions of the receptors that we are to consider in this chapter do not cease with insuring a favorable starting point for muscular activities. During locomotion equilibrium must still be maintained, a problem far more difficult than when at rest. The external stimulus which starts the locomotion does not guide this balancing feat nor insure the coördination of the large groups of muscles involved in flying or running; coördination and equilibrium are regulated during activity by stimuli arising from the constantly changing relation of part to part in the animal body or of the body as a whole to the earth. Because they record the changing relations involved in self-activity the receptors which initiate the important group of postural reflexes and furnish the afferent basis of muscular coördination, notably of locomotion but also of other activities, have been called *proprioceptors*.

This chapter will be devoted to the *proprioceptors*, the reactions that they initiate and the sensations that arise from them. The maintenance of posture and the regulation of the activities of skeletal muscles may be divided into two main phases, of which one concerns the relation of part to part in the body; the other, the relation of the body as a whole to the earth, or, more exactly, to the direction of the pull of gravity. Corresponding in general to these phases, we find two groups of receptors: (1) The *muscle sense receptors*, or *motoceptors*, stimulated by changes in the relation of parts; (2) the *non-acoustic labyrinths* stimulated by the position or, changes of position, of the body as a whole.

THE MOTOCEPTORS.

Experimental Proof of Existence. We will first consider the motoceptors. A frog at rest holds the hind legs in a very characteristic folded posture. It is easy to show that this posture is not dependent upon the brain or upon receptors in the head, since the position of the hind legs in a frog with the brain destroyed or even with the head removed is practically normal, despite marked changes in the posture of the body as a whole. If, however, the dorsal or afferent roots of the spinal nerves supplying one leg are cut, this leg never again assumes the normal posture, but, like the leg of a dead frog, lies as it falls. The motor impulses are, therefore, not central in origin, but arise reflexly in the leg concerned. Though glimpsed by Bell, this problem was first clearly seen by Claude Bernard, who showed that the locomotion of a frog was little altered by skinning—

a proof that the necessary receptors were not in the skin but in the motor structures. Sherrington (1894) was, however, the first to identify the receptors and to show their relations and significance. By nerve degeneration he proved that the so-called "motor" nerves to various muscles of the cat contain from one-third to one-half

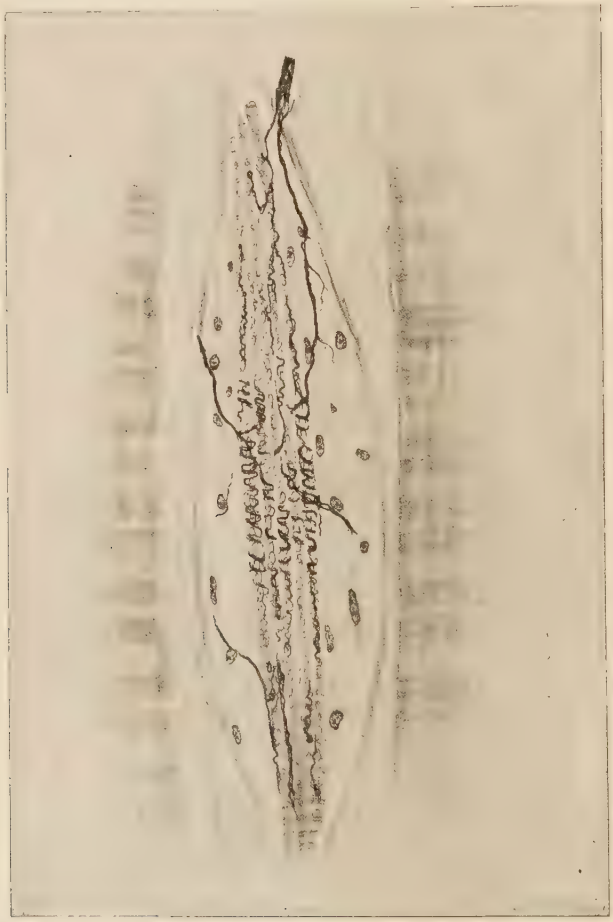

FIG. 52.—Muscle spindle *in situ*. On either side are ordinary muscle fibers; in the center a group of intrafusal fibers; at the top an afferent nerve enters to terminate in annulo-spiral endings around the intrafusal fibers. (From Schäfer's Essentials of Histology, by permission of the author.)

afferent fibers, that these fibers connect with a special type of receptor—the *muscle spindle*—in the muscles and that the stimulation of the central and of such a "motor" nerve produces reflex contraction or relaxation of other muscles.

The history of the sensory aspect of the motoceptors is similar to

that just given. It was once thought that the knowledge of the position of the arm, for example, arose from cutaneous sensations caused by the folding and stretching of the skin at the joint, or from an "innervation sense" connected with the motor discharges involved in willed movements. Since, however, complete insensitivity of the skin of the arm does not appreciably affect one's ability to tell its position or movement, whereas normal cutaneous sensations in the absence of sensations from the muscles do not enable us to do so, it is clear that the motoceptors rather than the cutaneous receptors give sensations of movement and position. Since the movement due to electrical stimulation of the nerve is perceived as clearly as voluntary movement, there seems to be no ground for the assumption of an "innervation sense."

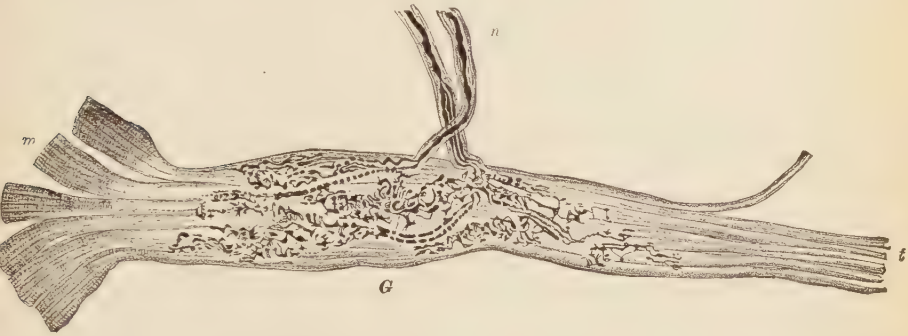

FIG. 53.—Musculo-tendinous organ of Golgi from human tendon of Achilles. *m*, muscle fibers; *t*, tendon bundles; *G*, organ of Golgi; *n*, nerve fibers. (From Schäfer's Essentials of Histology, by permission of the author.)

Structure of the Motoceptors.—We have presented proof that sensations of position and motion as well as reflexes of posture thus arise from the motoceptors located in the motor structures. These receptors include: (*a*) *Muscle spindles;* (*b*) *tendon spindles,* or *musculo-tendinous organs of Golgi;* (*c*) *modified Pacinan corpuscles;* (*d*) *articular end bulbs* and possibly other forms. The muscle spindle consist of small groups of striated muscle fibers of an undifferentiated type enclosed in a sheath and richly supplied with branching terminations of receptive neurons (Fig. 52). The musculo-tendinous organs occur at or near the junction of tendon and muscle and likewise represent a rich arborization of receptive neurons (Fig. 53). Modified Pacinian corpuscles are found about the end of the bones in connection with the articular ligaments and other structures of the joints. The articular end bulbs are found in the synovial membranes, particularly of the finger joints. All these receptors are thus from their structure and location well adapted to mechanical stimulation by changes in the tension of muscles and tendons and by changes in the relation of the parts of the limbs

at the joints. The relative importance of these different types of receptors is by no means clear, but since all the impulses apparently lead to similar results on both the reflex and sensory sides, no attempt will here be made to distinguish between them.

Reflexes.—The reflexes initiated by these motoceptors are varied and important, a fact reflected in the richness of connection of their afferent fibers with the cerebellum (page 695). Since, however, their influence on the postural reactions is intimately associated with other receptors, the reflexes will not be considered further until the non-acoustic labyrinth has been discussed (page 508). The *myotatic* reflex and its important relation to muscular tone will be considered later (page 691).

Sensations.—The sensations from the motoceptors are unique and important. They include (1) *movement*, (2) *force exerted*, (3) *pressure* and (4) *position*. Perception of motion or changing relation between movable parts is primary and of great significance. If one segment of a limb is moved with respect to a second segment or to the body, either voluntarily or involuntarily by electric stimulation of the motor nerve or by the hand of a second person, the motion is perceived if rapid or extensive enough. For the threshold of motion both rate and extent must be considered; the slower movement requires the greater arc and *vice versa*. A surprisingly small movement may be perceived, with ordinary rates the minimum perceptible arc seldom exceeds one degree. In general, active motions are better perceived than passive, and proximal joints, as the shoulder, are more sensitive than distal ones, such as the finger.

Even if no movement actually occurs we may be aware of the degree of *tension* developed in the muscles and tendons, as when we attempt to lift a heavy weight. If a series of unseen weights are lifted, the movement being in each case the same, the *force exerted* is very accurately perceived. In fact, it is through the lifting of weights that the most important data on the recognition of intensity have been obtained. The just perceptible increase or decrease in a weight bears to this weight a ratio, which for a considerable range of intensities, is approximately constant. For very light or very heavy weights discrimination is somewhat less keen. (See Weber's law, page 491).

The *pressure* of a foreign body applied to the skin causes deformation first of the skin itself and then of the subcutaneous and muscular tissues below. The effect of light pressures up to 6 or 8 gm. is confined to the skin; above this it is in part transmitted to the deeper structures. As a result, the majority of contacts encountered or employed in experiments, as for example in determining with a compass the degree of separation of the two points that can be perceived (page 525), have compound results, arousing both cutaneous and motoceptors. Henry Head and other workers have shown that

section of a cutaneous nerve and consequent complete insensitivity of the skin does not prevent the recognition of pressure and of variations in its intensity, the location of the point touched and, according to some, the perception of the two points of the compass, if the pressure used is sufficient to affect the deeper structures. Although the skin contributes sharpness of localization and fineness of discrimination to the sensory complex, the evaluation of pressure comes almost exclusively from the deeper motoceptors. If a fold of loose skin on the arm is grasped between the thumb and forefinger, so that only cutaneous receptors are affected, the contact is clearly felt, but when the pressure has exceeded a few grams further increase up to several kilograms causes little change in sensation, whereas if the entire arm is grasped, so that the force is transmitted to the underlying muscles, slight variations in pressure are instantly recognized.

It is clear from what has just been said that the recognition of the amount of force exerted in lifting a weight might depend not alone on the tension in the flexor muscles but also on the pressures upon the deeper tissues of the hand in which the weight rests.

The *position* of a limb, even though long maintained, is recognized. The recognition of position is, however, noticeably less keen than is that of motion. This is strikingly illustrated by the common experience of being in doubt as to the exact position of the arm on waking in the night. The slightest movement, even of the unconscious type associated with thinking about the arm, will cause its position to flash into sudden clearness.

The importance of muscle sense cannot well be overestimated. Within the reach of our arms and legs lies a bit of space which we know intimately from constantly repeated explorations. The objects within it do not indeed appeal to the muscle sense alone, but to the eye and skin as well; nevertheless, the knowledge of their position with relation to our bodies we owe to the muscle sense by which we have repeatedly measured the distances between object and object and between them and our bodies. Through the muscle sense alone do we directly perceive motion, its extent and force; if other senses carry spatial implications, as indeed most do, it is by virtue of their association with the muscle sense by which their sensations have become signs of motions that have been and may again be performed.

The skilled movements involved in writing, drawing and the use of all types of tools are possible only because the movements concerned can constantly be perceived along with their extent and force through the muscle sense. Although vision gives information that may be used in the guidance of movements it is inadequate for the uses of life, as shown by the disabling clumsiness of the sufferer from tabes in whom the muscle sense is partially lost.

THE NON-ACOUSTIC LABYRINTH.

The membranous labyrinth of the ear comprises two functionally distinct receptors. The cochlea is stimulated by sound waves; the remaining structures including the three *semicircular canals* arranged in the three planes of space and the *saccule* and the *utricle* belong to the proprioceptive system. It will be remembered that the *non-acoustic labyrinth*, as it may be called, contains five sensory areas, three *crista acoustica*, one in the ampulla of each canal, and two *maculæ*, one each in the *saccule* and *utricle*. All these areas contain hair cells, the hairs of which are imbedded in gelatinous masses, which in the maculæ are weighted by numerous dense *otoconia*, or *otoliths*.

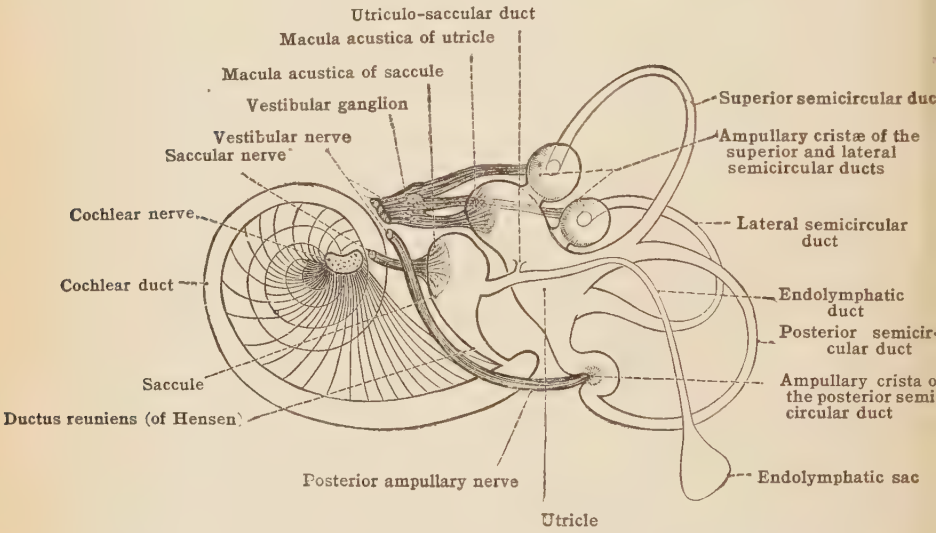

FIG. 54.—Diagram of the right membranous labyrinth and the divisions of the acoustic nerve as seen from behind. (Morris' Anatomy, P. Blakiston's Son & Co., Publishers.)

A well-developed non-acoustic labyrinth is present in nearly all vertebrates; phylogenetically it earlier reached a high state of development than did the auditory portion of the ear, which is conspicuous only in land vertebrates. An enormous mass of experimental work extending over many years[1] clearly shows the importance of the labyrinth, the main features of its function and the close integration of its impulses with those of other receptors concerned in equilibration, but fails to agree on important questions of the mode of stimulation of its various parts.

[1] The mere bibliography of the subject recently compiled by Griffith is a large volume.

Effect of Loss of Normal Impulses.—The absence of the impulses normally aroused in the labyrinth (from section of its nerve, its entire destruction, or complete anesthesia) causes a number of characteristic disturbances of posture and locomotion varying in kind and severity with the systematic position of the animal and its normal mode of locomotion—whether crawling, walking, swimming or flying. In general, these disturbances are more severe in the more difficult activities of flying or swimming than in walking, and less severe and lasting in mammals than in lower forms. In the shark, if one labyrinth is destroyed the eyes and fins assume asymmetrical positions which at first interfere with locomotion and cause abnormal positions of the body but later are less marked. If both labyrinths are destroyed the asymmetric positions of the eyes and fins do not appear. The animal, however, unlike the normal shark, does not resist being turned on its back in the water and will swim off in that position.

In mammals asymmetric positions and often rolling movements occur after the destruction of one labyrinth. When both are destroyed most mammals are at first unable to stand, although in time a considerable degree of compensation takes place and they are able to walk.

Labyrinthine Reflexes.—If a normal shark is rotated certain reactions appear which are not present in animals without the labyrinth, and therefore must be initiated by it. Rotation around the longitudinal axis, for example, with the right side down and the left up, causes an upward movement of the right and a downward movement of the left eye. At the same time the right pectoral fin moves down and the left up, both more markedly at their posterior borders. It will be seen that the movements of the eyes are such as will keep them looking in the original direction, and the movements of the fins are such as tend to resist the rotation or restore the original position. In mammals, including man, similar compensatory eye movements occur upon rotation as well as movements of the limbs tending to maintain the original position of the body. These findings have been checked in a number of animals by direct stimulation of the labyrinth, so that there can be no doubt that the non-acoustic *labyrinth is a receptor stimulated by the movements and the position of the body in space and that it initiates reflexes tending to maintain or restore the habitual posture of the body and to maintain the existing relation of the retinæ to the images falling upon them* (page 672). The labyrinth is thus a typical proprioceptor.

Nystagmus.—In man, because of the importance of the eyes, their compensatory movements have received much attention, and one phase, after-nystagmus, has had its biological significance obscured by its isolated use as a test of fitness in aviation. These compensatory movements in man are of the type already mentioned. If the

head is slowly rotated either actively or passively, for example, to the right, the eyes will be seen to move to the left at an equal rate, with the result that the eyes continue to "look" in the same direction, and the confusion of moving images on the retina is avoided. If the rotation of the head is continued it is clear that the eyes would soon come to the limit of possible motion to the left. Before this occurs there is a quick movement of the eyes to the right, after which the slower compensatory movement to the left is resumed. With continued rotation to the right the alternate movements of

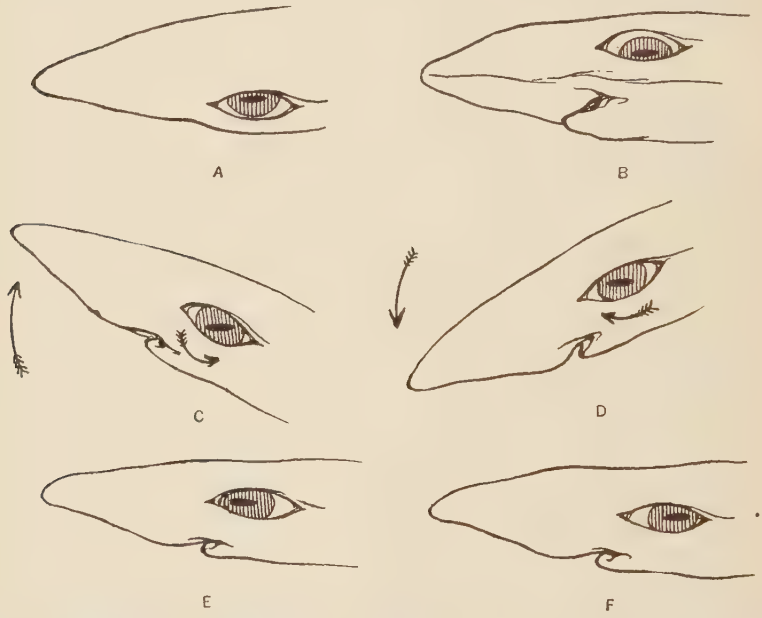

FIG. 55.—Diagram of compensatory positions of the eye in the dogfish. *A*, rotation to left and, *B*, rotation to right around longitudinal axis; *C*, rotation head upward and, *D*, rotation head downward around transverse axis; *E*, rotation to left and, *F*, rotation to right around dorso-ventral axis. (Maxwell's Labyrinth and Equilibrium, J. B. Lippincott Company, Publishers.)

the eye, or *nystagmus* (slow to the left, fast to the right), continue for a time, but finally fail and along with them the sensation of continued rotation (provided the eyes are closed). If now the rotation is slowed or stopped the alternate slow and fast eye movements reappear, but in the opposite sense, that is, with rotation to the right, the slow phase, instead of being to the left, is to the right. These movements, the *after-*, or *post-rotational*, *nystagmus*, continue for from ten to fifty seconds, the time equaling that of the initial nystagmus if the retardation was at the same rate as the previous

acceleration. This duration corresponds to an illusion of rotation in the direction opposite to the previous actual rotation. Nystagmus occurs in the dark or with the eyes closed, although vision may modify these movements, it is not essential to them. They cease after the destruction of the labyrinth and may be provoked by its direct stimulation; they are, therefore, labyrinthine reflexes. It has recently been shown that after-nystagmus may be greatly reduced or almost entirely abolished by repeated rotations—this has been shown with laboratory animals and occurs with acrobats and whirling dancers.

After-nystagmus is, therefore, to be looked upon as a response to retardation just as the initial nystagmus is a response to acceleration; change of motion being here the essential stimulus, another instance of what has been said of stimuli in general (page 488). The physical conditions with regard to inertia (by which we assume the labyrinth to be stimulated) are the same for a retardation from a previously uniform rotation to the right, as for an acceleration from rest to the left, and it is not surprising to find the response of the organism the same. In the ordinary experience of man and animals rotations are brief and of a few degrees only whirling chairs are not part of the normal environment. When extensive rotations are included in the daily experience after-nystagmus is reduced, an adaptive response.

Method of Stimulation.—How is the labyrinth stimulated? By its deep position in the head it is effectively screened from all ordinary external stimuli. Since it contains structures of distinctly different densities, and since it is stimulated by the position or changes in the position of the body, it has been assumed that these changes in position cause relative movement of the different structures or that under the pull of gravity the relative position of the structures differs with the position of the body resulting in appropriate mechanical stimulation of the contained receptors.

This view receives support from the study of an analogous receptor in certain invertebrates—the statocyst. Here it has been shown that the point of contact of a dense statolith with the sensitive walls of the containing sac varies with the position of the animal and hence for each position different cells are stimulated and different reflexes follow.

The general view that the stimulation of the labyrinth is mechanical and depends upon the inertia of some of its parts is undoubtedly correct, but the detailed accounts of its workings as often given outrun our knowledge and contain some distinct errors. For example, it is assumed that when the head is rotated there is a flow of the endolymph in the semicircular canal or canals lying in or near the plane of rotation, which stimulates the projecting hairs of the associated crista, and that the duration of the after-nystag-

mus corresponds to the flow of the endolymph, which from its inertia follows the stopping of rotation. The facts are, however, in conflict with this view. It was pointed out long ago by Mach that the internal friction in such minute tubes would prevent an appreciable flow. The duration of after-nystagmus is reduced by training; this effect could not be expected if it depended upon a purely physical process. Most important, Maxwell has shown that the horizontal canal in the shark may be ligatured, cut and turned at right angles to its original position and still give normal reactions to horizontal rotation, although no movement of fluid is possible.

Recent work has thrown doubt on the distinction of function between different parts of the labyrinth; the utricle and saccule are not wholly static nor are the canals wholly dynamic. Further analysis is premature and can only hinder progress.

Sensations.—Turning from the labyrinthine reflexes to the sensations the situation is no less controversial. It is clear that we are aware of changes in position that at the same time produce reflexes from the labyrinth. The present view of workers in this field is that the sensations come not directly from the labyrinth, but from the perception through the muscle sense of the movements reflexly produced.

Maintenance of Posture.—The maintenance of posture is a complex activity and not wholly dependent on any one receptor. Maxwell, for the shark, Magnus, for the rabbit, and Kleitman and Koppányi, for the fowl, have given us very complete and instructive pictures of the mechanism involved. It is in the main threefold, resting on the two types of proprioceptors (muscle sense and labyrinth) and on the cutaneous receptors stimulated by contact with the support. When in the air or water this last naturally fails. In addition, vision, and to a minor extent hearing and possibly some of the visceral receptors, contribute to the complex.

The normal shark, as we have said, rights itself promptly if turned belly up in the water; the labyrinthless shark may be turned into any position without offering resistance, but if allowed to swim away, promptly assumes the normal posture if it comes in contact with the bottom. The upright position of the shark is thus insured by two reflexes, the first from the labyrinth and the second from the stimulation of certain areas on the snout and fins. A third reflex resulting from the asymmetric tension of the body musculature when the body is bent to one side results in movements of the eyes, but has no apparent effect on posture.

Magnus has shown that if a rabbit deprived of the cerebral hemispheres but with the mid-brain intact is held on the side in the air, so as to avoid as far as possible the stimulation of the skin by contact with any support, the head will assume the normal position in consequence of the *labyrinthine reflex*. The head now being erect,

whereas the body is on the side, the asymmetric tension of the neck muscles serves as the stimulus for a *neck reflex* which will bring the body into normal position if it is free to move. These reflexes naturally fail in a rabbit deprived of its labyrinths, but if such a rabbit is placed on its side on a table the head is also raised to the upright position. This is a cutaneous reflex arising from the asymmetric stimulation of the skin by contact with the table. It fails if a block of wood is placed on the upper side of the animal to balance the stimulation of the table. When the head reaches the upright position the normal posture of the body is completed by the neck reflex. The asymmetric stimulation of the body may, moreover, act directly upon the body to cause assumption of the normal posture.

In the intact rabbit, therefore, the normal posture is insured by two distinct chains of reflexes, one initiated by the labyrinth and the other by the skin and both completed by the muscle sense. This well illustrates the complexity underlying so apparently simple an act as the sitting upright of a rabbit. Impulses from many sources are organized and converge upon the muscles of the limbs, neck and trunk that maintain posture. An essentially similar series of reactions occurs in the fowl. Since the proper and rapid integration of these impulses in the central nervous system is the important feature of equilibration, mammals with their more highly organized nervous systems recover more completely than lower forms after the loss of the labyrinths. They may be able to walk and run and, if undisturbed, show little difference from normal animals. Under excitement, or the necessity for active movement, however, they often break down into an *ataxy* (incoördination of movement) almost as severe as that immediately following the operation.

Summary.

Posture is maintained and locomotion is accomplished by reflexes initiated from the *proprioceptors*, which are stimulated by changes in the position of the body or in the relation of its parts. The proprioceptors are of two types, *motoceptors* and the *non-acoustic labyrinths*.

The motoceptors are found in the skeletal *muscles* (muscle spindles), the *tendons* (tendon spindles) and about the *joints*. Their receptive neurons are found with the efferent neurons in the so-called "motor" nerves to the muscles.

The motoceptors are mechanically stimulated by changes in *tension* of the *muscles* and *tendons*, by changes in *position* of the *joints* or by *pressure* from without if sufficient in intensity to reach beyond the skin.

Their stimulation initiates reflex changes of *tone* or *contractions*,

which maintain the relation of part to part in posture or bring about some of the movements of locomotion, and causes sensations of *movement, tension* or *pressure* or of *position* of the part involved.

The sensations from the motoceptors are the basis of all space perception and hence of great psychic importance.

The non-acoustic labyrinth is stimulated by the relation of the position of the head to the pull of gravity or by changes in this relation. The stimulation is apparently mechanical and depends in some manner not clearly understood on the different density, and therefore inertia, of its various parts.

Stimulation of these receptors initiates *reflexes* maintaining the *posture* of the entire body and apparently indirectly sensations of position and movement.

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CHAPTER XXXII.

CUTANEOUS RECEPTORS.

The great majority of the somatic receptors, unlike the proprioceptors considered in Chapter XXXI, are stimulated by objects external to the body, and for this reason have been called *exteroceptors*. Such stimuli play most directly upon the surface of the organism, and it is significant that not only the great majority of the receptors, but even the nervous system itself, take their origin from the ectoderm. Leaving aside the eye, ear and olfactory organ (all of ectodermal origin), we find the skin covering the entire body, together with the associated mucous surfaces of ectodermal origin, thickly studded with a variety of receptors, the total number of which runs into the millions. In this it stands in marked contrast to other parts of the body, for in none of the other tissues are found so many or so varied receptors, or such ample afferent pathways as measured by actual number of nerve fibers. And to make the contrast the more striking, the receptors of the skin give rise to vivid sensations, whereas many of the receptors in the deeper tissues, though initiating reflexes, give rise to impulses which appear in consciousness only vaguely if at all.

The exteroceptors fall readily into two main groups. One includes the so-called special sense organs (eye, ear and olfactory organ) which are of such great sensitivity as to respond to the weak stimuli from sources at a distance from the body and hence are called *distance receptors;* the other includes the more widely scattered and simpler receptors which, because of their lesser degree of sensitivity or the nature of their customary stimuli, are stimulated only by objects in contact with the body and hence are called *contact receptors*. It is to such of the latter as are found in the skin, and which therefore may be called *cutaneous receptors,* that we will give our attention in the present chapter.

By the earlier workers the skin was looked upon as a continuous sensory surface, from which arose sensations of "touch," in which, however, different qualities could be distinguished. It was not until 1850 that the presence in the skin of numerous receptors of several types was established by careful experimentation. The evidence for the existence of separate receptors with separate conduction paths may be summarized briefly. If the skin is explored with very small objects, and care taken that the stimulation is actually

confined to small areas, its sensitivity is found to be punctiform and not continuous. Thus, a pointed metal rod cooler than the body drawn lightly along the skin gives rise to cold sensations at certain definite points only; a warm rod, to sensations of warmth at certain other spots; a stiff hair, to sensations of touch (contact) at still other spots; a needle, to sensations of pain at spots which, though more numerous, are, according to most observers, distinct. Evidence of separate conduction paths is furnished by the effect upon sensations of injuries to the spinal cord. There is satisfactory clinical proof that lesions of the cord may cause the loss of any of the four types of sensations mentioned above (cold, warmth, touch or cutaneous pressure and pain) without impairment of the other three, or that any three may be lost and the fourth retained. Study of the results of injuries to peripheral nerves by Head and others has emphasized the distinction already pointed out (page 502) between the cutaneous and the "deep" or proprioceptive sensations.*

In addition to the four kinds of receptors mentioned as established by evidence of the above type, others have been claimed by certain investigators; the evidence regarding receptors for *tickle* and *vibration* will be discussed later.

TEMPERATURE RECEPTORS.

From extensive explorations of the skin for points from which sensations of cold can be obtained, the number of such "cold spots" has been estimated at 12 or 13 per square centimeter or a total for the entire body of 250,000. The "warmth spots" are less numerous, being estimated at 1 to 2 per square centimeter, or a total of 30,000. The nervous structures corresponding to these temperature-sensitive "spots" are not known with certainty. Those for cold are thought to be the end bulbs of Krause for the following reason: From the center of the cornea of the eye sensations of pain alone are obtained; from the margin, pain and cold, but no others. The nervous structures present are the "free" intra-epithelial nerve endings found in all parts of the cornea and the end bulbs of Krause found only at the margin; the former are thus inferred to subserve pain, the latter cold. On similar, but less satisfactory, evidence the corpuscles of Ruffini are thought to be the receptors for warmth.

Physical Situation in Skin.—In discussing the probable mode of stimulation of the temperature receptors and their significance to the organism, we must bear in mind the physical situation as it affects the flow of heat in the skin. In birds and mammals, including

* Head's further division of the cutaneous sensations into protopathic and epicritic on the basis of differences in their reappearance during regeneration has not been supported by subsequent experimentation or by clinical observations.

man, the interior of the body is at a constant temperature usually well above, though occasionally slightly below, that of the surrounding air. There is thus normally a temperature gradient between the interior of the body and the air. Along this gradient outward through the skin of man at rest there flows on the average 1800 Calories in twenty-four hours, or 0.00375 gram calories per square centimeter per hour, though at active work the heat loss may be doubled (page 463). This heat loss is, of course, more rapid from the exposed skin of the hands and face than from the skin covered by clothes, since these retain a warmed layer of air in contact with the body and thus markedly reduce the steepness of the gradient.

FIG. 56.—End-bulbs (of Krause) in human conjunctiva. (From Schäfer's Essentials of Histology, by permission of the author.)

The general situation may be diagrammed as in Fig. 57. Here the horizontal scale represents the distance beneath or outside the surface of the skin, and the vertical scale the temperatures found at these points. If, for example, an air temperature of 16° C. has existed for some time, a physical equilibrium will have been reached and temperatures similar to those shown along the gradient will be found by exploration at the different distances within and without the skin surface. If now the air temperature is lowered to 8° C. the increased temperature difference will cause an increased heat flow outward and the temperature of the skin will fall. Since regulative changes in blood flow and the like promptly occur in the skin, the alteration in the gradient is not like that of a simple

physical system; nevertheless, a new equilibrium is soon reached with temperatures which may be diagrammatically shown along the line beginning at 8° C. It is clear that the skin will have suffered a fall in temperature greatest at the surface but extending far beyond the depth (0.1 to 0.2 mm.) at which the receptors lie. In the same way a rise of air temperature, for example to 24° C., will reduce the heat loss and raise the temperature of the receptors. The physical results, then, of a rise or a fall in the temperature of the air is a shift upward or downward in the temperature of the receptors. This change, rapid at first, soon slows down and the receptors come to rest at a new and constant temperature.

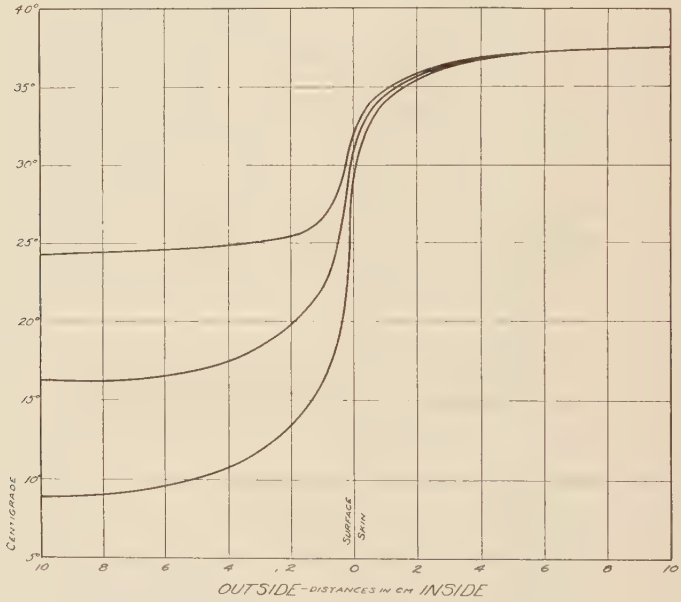

FIG. 57.—Temperature gradient in skin and surroundings.

Responses to Changes of External Temperature.—What are the responses to such changes? If we sit for a time in still air at any temperature within the range ordinarily experienced, its contact with the skin does not give rise to any sensation either of warmth or of cold nor to any reflexes. If now the temperature is lowered and kept at a new level two results follow: (1) We experience a sensation of cold, distinct in the beginning, but fading back into indifference in the course of a few minutes; (2) certain reflexes appear. If the temperature of the air is raised a similarly transient sensation of warmth is experienced and characteristic reflexes again

appear. From this we may safely infer that a change in the temperature of the receptors is their proper stimulus; this is in accord with the general conception of the stimulus already discussed. The change must exceed a certain rate to be effective; water must be heated at least 0.2° C. per minute to feel warm to the finger immersed in it, or be cooled at least 0.15° C. per minute to feel cool.

Indifferent Temperature.—If a series of beakers containing water at varying temperatures is tested with the finger one may be selected that feels neither warm nor cool; this water is said to be at the *indifferent temperature*. This water clearly has the same effect as the air to which for a time the skin has been exposed; its temperature will, however, be found to be higher than that of the air. Since neither the air nor the water causes a sensation, the water evidently does not alter the gradient established by the air; that is, it receives heat at the same rate as did the air. The greater heat capacity and conductivity of the water enable it to do this at a temperature nearer that of the body. In the same way any substance will give a characteristic indifferent temperature corresponding to its physical properties. For example, the head of a hammer will feel cold while the handle feels indifferent, although both are at the same temperature, because of the greater conductivity of the metal. The physical effect of air varies not alone with its temperature, but with its content of water vapor and its movement. For this reason the thermometer gives no sure indication of the physiological effect of air, and the Hill katathermometer, which measures its cooling power, is a more significant instrument in the practical problems of ventilation.

Adaptation.—As we have said, a change in the external temperature causes a change in the temperature of the receptors and a sensation of warmth or cold, as the case may be, which does not persist, even though the new external temperature be maintained. The duration of the sensation is greater the greater the alteration of temperature, but changes of even 20° C. on limited areas of the skin cannot be felt longer than three minutes. Is this fading out of the sensation due to fatigue of the receptors or to adaptation? (page 491). To this a clear answer may be given: If the finger is immersed in water at the indifferent temperature, and the water heated or cooled above the minimum rate necessary for stimulation, the sensation may be prolonged for over forty minutes, showing that the receptors are not fatigued, even after continuous activity, for more than twelve times the duration of the sensation following a single change of temperature. Again if heat be applied intermittently as often as once a second it is felt each time over a long period. Since the dying away of the sensation does not leave the receptors any less sensitive to further changes of temperature, it cannot be the result of fatigue, but must be considered a true

adaptation. Indeed, adaptation is better exemplified by the temperature receptors than by almost any of the others. Adaptation occurs readily and naturally over the range of temperature ordinarily encountered, but, as everyone knows, there are limits above and below which adaptation does not occur, even after long exposure; we continue to have sensations that have an element of warmth before an open fire, or of cold on a winter day. The range of possible adaptation varies in different parts of the skin; it is said that the thigh may be adapted only for 28° to 30° C., a range of 2° C.; the back of the hand for 23° to 33° C., a range of 10° C.; while the finger has a range of 28° C., being capable of adaptation to 11° and to 39° C.

In the absence of knowledge of how changes of temperature develop nerve impulses in the receptors, and indeed of what histological structures constitute the receptors, speculations as to how adaptation is brought about and what constitute the limits to adaptation are not apt to be profitable. Adaptation would seem to require: (*a*) That the receptors respond only to *changes* in temperature; (*b*) that a new physical equilibrium with a new and stable receptor temperature tend to follow the change of external temperature. We have seen that both of these are probable. That such a physical equilibrium is involved is indicated by a number of experimental results. As we have said, the time required to establish adaptation increases with the amount of the temperature change, which would be true of establishing a new physical equilibrium. On the other hand, the reaction time is less the greater the change of external temperature corresponding to the greater speed with which an extensive change would alter the temperature at the receptor. A greater external change would be expected to cause an earlier disturbance of the physical conditions but require a longer time for a complete readjustment. That a relatively slow process such as heat transfer in the skin is involved, is indicated by the low rate needed to distinguish intermittent stimuli. This varies from 1 to 4 per second, while other receptors may give separate sensations at rates from 25 to over 500 per second.

The most careful and extensive work indicates that the limits of adaptation in the finger are really set by the points above and below which heat and cold cause pain which, as we shall see, are at about 45° and 10° C. Thus adaptation is only possible within the range giving us pure temperature sensations.

The Intensity of Temperature Sensations.—Different regions of the body differ markedly in their sensitivity to heat or cold. Thus an object feels colder or warmer to the skin of the abdomen or to the nipple than to the fingers or face, yet curiously the power of discriminating slight differences in temperature is far greater for the finger than for the nipple. Whether these differences are due to

differences in conductivity for heat or other physical peculiarities of the skin or to the number and character of the receptors is not known. In any given region the intensity of the sensation increases as more surface is involved. This may be due in part to purely physical causes but the effect of the greater number of receptors involved and possibly some form of summation in the central nervous system are probably more important.

If an object in contact with a given area of skin is heated above or cooled below the indifferent temperature the sensation becomes more and more intense as the temperature difference becomes greater. The physiological changes corresponding to this are not as simple as might be expected, and on certain points all investigators are not in agreement. It is probable that the weakest stimuli excite only those spots that, because of their position or nature, are more sensitive, so that for a time the increasing intensity of the stimulus increases the number of active receptors in the area. This view is made probable by the fact that when the spots are tested separately great differences in sensitivity are found. After all the receptors in the area in question are called into play further increase in the stimulus may involve other receptors in the immediate neighborhood through the ready lateral diffusion of heat. That this actually takes place is indicated by the effect of anesthetizing a ring about the area tested.

Still further increase of heat leads to a sensation usually called "hot," which seems to differ subjectively from a more intense warmth, and finally to a "burning hot" which is painful. It is known that the cold spots may be stimulated by temperature of 37° to 45° C. without, if proper precautions are taken, causing any sensations of warmth. It is usually thought that this regularly occurs with higher temperatures and that "hot" is a compound sensation or "fusion," to which both the warmth and cold spots contribute. When temperatures of 35° to 50° C. (average, 45° C.) are reached the pain receptors are stimulated and the character of the fusion again changes; with further increase of heat, pain rapidly becomes the dominant feature. With a lowered temperature pain appears at about 10° C., but whether the warmth spots are normally involved in cold stimulation is not clear. The following table,

Sensations.	Warmth spots.	Cold spots.	Pain spots.	Approximate temperatures.
Burning hot	+	+	+	45.0
Hot	+	+	0	40.0
Warm	+	0	0	30.1
Indifferent	0	0	0	30.0
Cold	0	+	0	29.9
"Biting" cold	0	+	+	10.0

The activity of a receptor is indicated by +, its inactivity by 0. The temperatures, given in round numbers, are illustrative only and would vary with the level of adaptation.

modified from von Frey, indicates the probable relation of these three types of receptors in producing the large range of temperature sensations experienced—a coöperation apparently unique among receptors.

Relation to Temperature Regulation.—We have thus in the temperature receptors, organs situated in the critical part of the heat gradient over which flows a large part of the energy produced in the body. They are stimulated by changes in their temperature caused by changes in the heat loss that follow changes of external temperature. The presence of receptors for both warmth and cold insures that changes of the environment in either direction will cause stimulation, and their power of adaptation permits such stimulation to occur at a variety of temperature levels. Such an apparatus constitutes a poor thermometer in a physical sense, having no fixed zero nor other reference point and often giving contradictory reports on different occasions to the same temperature, but regarded as an indicator of the relation of a warm-blooded animal to its surroundings it is admirably adapted to record those changes tending to upset the temperature equilibrium. It is not surprising, therefore, to find the temperature receptors intimately concerned in temperature regulation; in this, indeed, lies their significance to the organism.

As pointed out in discussing temperature regulation (page 447) a fall of temperature stimulates the heat center producing changes tending to conserve heat or increase its production while a rise leads to changes favoring the more rapid dissipation of heat. Of these the vaso-motor and postural changes follow so promptly upon exposure to cold as to indicate that the response of the center is directly dependent upon the stimulation of the warmth or cold receptors. It is interesting to note that in our skin the cold receptors are the more numerous, the more superficial, respond to a less rate of change (perhaps because of their position) and lead to better marked reflexes suggesting that cold is a condition more to be guarded against than is heat.

MECHANICAL STIMULATION OF THE SKIN.

The skin is exposed to a variety of mechanical stimuli and to these it is very sensitive. In considering the action of such stimuli the physical situation must be held in mind. Although the skin, as we have pointed out, is the region of the body most abundantly supplied with receptors, it is by no means wholly a sensory organ, but has other important functions which are reflected in its physical nature. In a land-dwelling vertebrate the skin is protective, preventing undue evaporation of body fluids and mechanically shielding the underlying structures as well as resisting the entry of harmful microörganisms. Corresponding to this the surface layer of the

epidermis, although thin, is remarkably firm and elastic, differing strikingly from the deeper layers of the epidermis and from the underlying true skin which, although strongly formed of connective tissue is more loose in texture and contains more fluid, so that limited deformation is relatively easy. The cutaneous receptors all lie below this first protective barrier imbedded in the Malpighian layer of the epidermis or in the true skin and, therefore, not directly accessible to the various physical forces playing upon the organism. The contact of a solid body with the skin causes a deformation of its surface and changed pressure relations in its deeper layers. As we have seen, pressures exceeding 6 to 8 gm. affect not only the deeper cutaneous receptors but also those of the muscles or other structures within (page 502). Since many of the contacts felt involve a force of less than 1 gm. the study of the amount of these pressure changes, the area affected, the resulting movements of fluids or other effects—what might be called the micromechanics of the skin—represents an extremely difficult problem concerning which we are almost entirely ignorant.

Evidence for Separate Mechanically Stimulable Receptors.—Mechanical stimuli regularly cause excitation of at least two, and, according to some investigators, of three or possibly of four types of receptors, and give rise to a corresponding number of sensations or different kinds of reflexes. The receptors are those for *touch* and *pain* and possibly for *tickle* and *vibration.*

As regards the first two we have already given evidence from interference with their paths in the cord that they are separate and should be ranked as distinct senses. Since this is so at variance with the general and natural view, that pain is the result of overstimulation of any receptor, it may be well to outline additional facts concerning the peripheral apparatus, which even in the absence of the above data would prove them to be independent. The threshold for mechanical stimulation of pain is far higher than that for touch (page 474); for areas of 3 to 12 sq. mm. von Frey has shown it to be one thousand times as great, although for very small areas, such as the point of a needle, there is little difference. The response to the stimulus is more prompt for touch, the sensation of pain particularly near the threshold developing slowly. As a result the reaction time for pain is from one and a half to seven times as long as that for touch. This difference is even more marked with the cessation of the stimulus; the sensation of touch ends promptly but pain persists. Since the sensation of pain arises slowly and outlasts the stimulus, the effect of repeated stimuli soon becomes continuous; thus, with electrical stimuli pain is continuous at 20 per second while touch does not fuse until 120 per second. Mechanical stimuli if effective, cause in the center of the cornea, the dentine of the teeth and the tympanic membrane

only pain, but no sensation of contact. On the other hand, a part of the inside of the cheek is said to be insensitive to pain, although contact is recognized. A very striking and important difference lies in the production of reflexes; protective reflexes are always conspicuous with cutaneous pain, whereas if any reflexes arise from touch alone they are inconspicuous. Again among the cutaneous senses the power of localization is most accurate for touch and least so for pain.

Concerning the other two, tickle and vibration, we have not the data on which to base a satisfactory decision. A *vibration sense* responding to the rapidly repeated mechanical stimuli of a tuning fork in contact with the skin has been claimed by some workers and is supported by limited clinical evidence indicating that it may be lost without impairment of touch in some diseases affecting the cord. Since this might be the result of an altered conduction or of an altered physical condition in the skin over affected muscles, it seems better not to separate vibration from touch.

Regarding *tickle*, more data are available, but the opinions are widely at variance and confusing. Cutaneous tickle (not deep tickle evoked from firm moving pressure along the ribs or under the arms, the sensation so fearsomely delightful to children) has been regarded variously as a separate sense, as related to pain, and has been divided into two factors, one of which is a by-product of touch, the other of pain. Although the status of the sense is controversial, the reflexes involved are important and interesting. Very slight mechanical stimuli, such as drawing a hair or wisp of cotton over the skin, evoke from certain regions, particularly the neighborhood of the nostrils and the entrance to the external auditory meatus, persistent unpleasant sensations and surprisingly strong reflex tendencies to shudder or shiver and to scratch the skin involved or brush the object away. It is obviously related to the "scratch reflex" of cats and dogs extensively studied by Sherrington and is a protective reflex that serves against crawling insects.

STIMULATION OF TOUCH.

We will first consider *touch* (contact, cutaneous pressure) and then *pain*. As has been indicated, the contact of a pencil point or similar object will cause a pressure disturbance in the skin which readily may be observed to spread over an area of a square centimeter or more. Tested thus, all parts of the skin give sensations. In order to control the amount of force applied, and to restrict it to a known small area, a different method must be used. The simplest and most satisfactory device is that introduced by von Frey, who utilized short horse hairs mounted in light handles. The force exerted can be determined by pressing down on the pan of a suit-

able balance; large or short hairs are stiffer and long or small hairs more flexible; the area of the cut end may be measured under the microscope. The application of hairs bending at 0.75 or 1 gm. is usually felt in all parts of the skin. Hairs of 100 to 200 mg., however, are felt at some points but not at others.

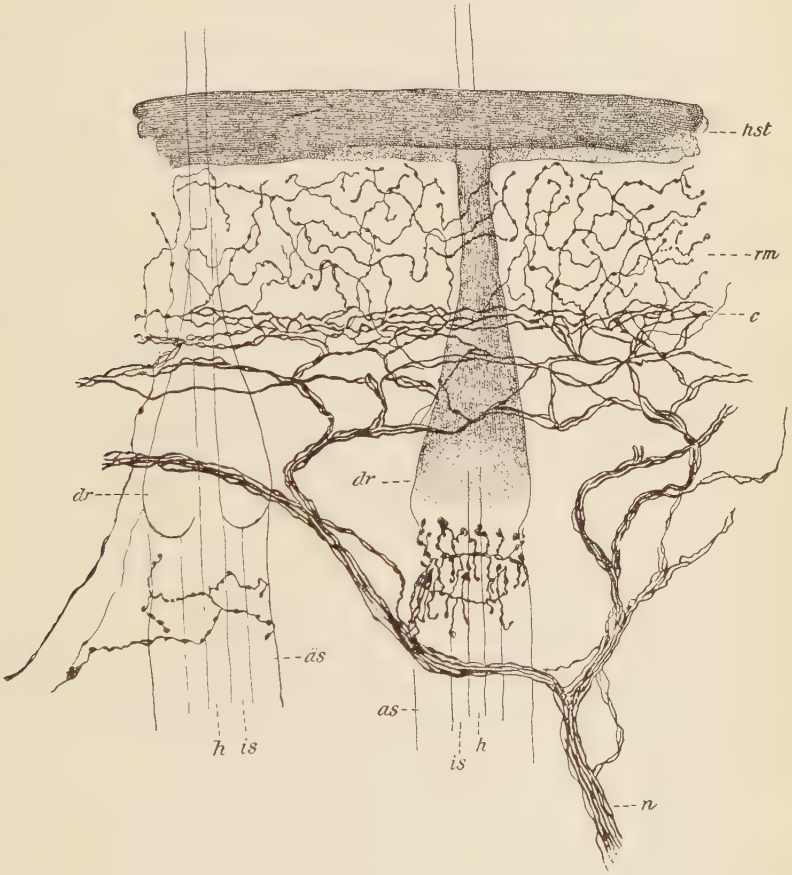

FIG. 58.—Nerves and nerve endings in the skin and hair follicles. (After G. Retzius, Biol. Untersuch., Stockholm, Bd. iv, 1892, Taf. xv, Fig. 4.) *hst*, stratum corneum; *rm*, stratum germinativum Malpighii; *c*, most superficial nerve-fiber plexus in the cutis; *n*, cutaneous nerve; *is*, inner root sheath of hair; *äs*, outer root sheath; *h*, the hair itself; *dr*, glandulæ sebaceæ.

Touch Spots.—Explored with such hairs numerous points are found which are sensitive to pressure; these have been called *touch spots* (contact spots, pressure spots). A hair bending at 100 to 200 mg. produces a pressure change of effective intensity for only a short distance about the point of application; applied directly

above the receptor it causes stimulation, applied elsewhere the pressure changes reach the nearest receptor in such reduced intensity as to have no effect. The number of spots found by this method is very varied, ranging from 9 per sq. cm. on the calf to well over 100 on the finger tips, where the spots lie so close as to make separation difficult. The average may be taken as 25 per sq. cm., which gives a total of 500,000 for the limbs and trunk.

The identity of these receptors, in contrast to those for temperature, are known with accuracy. They are of two types. On haired surfaces, which include about 95 per cent of the body area, a touch spot can always be found on the "windward" side of each hair, that is, directly over the follicle. Each hair follicle is supplied with nerve fibers which enter just below the sebaceous glands, form

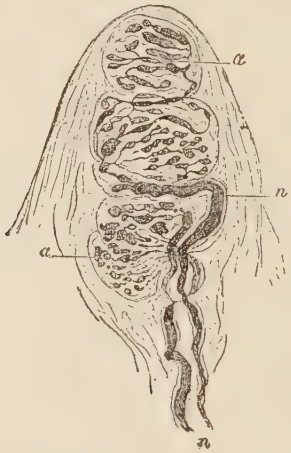

FIG. 59.—Tactile corpuscle in a papilla of the skin of the hand. (Ranvier.) (From Schäfer's "Essentials of Histology," by permission of the author.)

a ring and branch extensively. A touch at this point causes not only a sensation but a perceptible movement of the hair, and likewise all movements of the hair which are not mere bendings of the shaft cause sensations. The hair acts as a tiny lever, with its fulcrum at the point where the epidermis is pierced, intensifying pressure applied to its shaft. In many animals there are special tactile hairs or vibrissæ (the "whiskers" of the cat) with stiff shafts particularly fitted to act as levers and a rich nerve supply which make them important sense organs. A few touch spots, about 3 per cent, without connection with hairs are found on haired surfaces. On hairless surfaces, the palms of the hands and the soles of the feet, there are numerous touch spots which agree in number and distribution with the *tactile corpuscles* (Meissner's corpuscles).

Nature of Stimulus.—The effective stimulus is a certain degree of deformation of the skin at a rate which exceeds a certain minimum. Pressures which do not deform the skin are not felt. Thus the evenly distributed atmospheric pressure on the entire body surface causes no sensation though it is five hundred times that effective

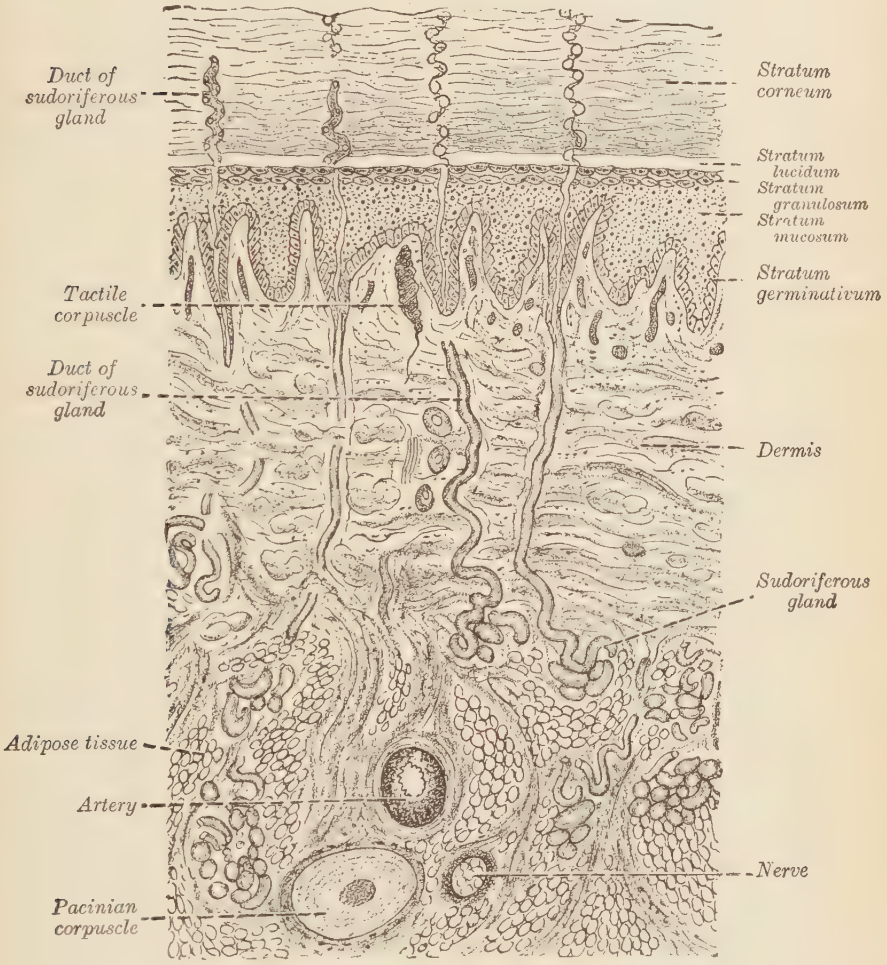

FIG. 60.—Tactile corpuscle in papilla of corium. (Gray's Anatomy, Lea & Febiger, Publishers.)

for small areas, nor are its variations from day to day felt, or the changes in pressure due to rapid ascent or descent in an elevator. In a similar way the pressure of water or mercury is not noticed by the finger or hand thrust into it except at the surface where the

abrupt change from air to liquid pressure causes a deformation. The deformation may be from pressure or from traction, as the pull on a bit of adhesive tape: both cause sensations and, if the movement is not great, they cannot be distinguished.

With the area so small that deformation readily occurs a normally effective pressure may be applied so gradually as to cause no sensation.

The threshold thus varies with a number of factors. The degree of deformation depends on the force, the area to which it is applied and the nature of the epidermis at the point, the rate of deformation is determined by the rate at which the pressure is applied. The exact laws governing the relationships among the factors are complex and imperfectly known. In general, if the other factors are constant, the greater pressure, the more rapid application of pressure and the smaller area are more effective.

Here, as in the case of the temperature receptors, we are ignorant of how the pressure changes are converted to nerve impulses. The only hypothesis of importance is that of von Frey, who assumes that the increased local pressure causes a movement of water through membranes, such as those of the tactile corpuscles, which are impermeable or only partially permeable to substances in solution in the cells. The concentration of these substances will thus be raised in the space about the nerve endings which will then be stimulated physico-chemically. He maintains that this process would account for the continued activity of the receptor under pressure, an effect not produced by direct mechanical stimulation of a nerve trunk.

Adaptation.—Adaptation occurs with touch as well as with the temperature senses. We cease to feel continuous uniform pressures; familiar examples are furnished by the contact of clothes, glasses, rings and other articles worn. Near the threshold, adaptation is very marked; a light von Frey hair is felt only as fleeting sensation unless it is moved after being set down. Even pressures of 160 gm. on an area of 50 sq. mm. may disappear in less than one minute.

Intensity.—If the pressure on the skin is varied, changes of intensity in the sensation will be noted. The ordinary discrimination of weights, however, whether placed on the resting skin or lifted, does not depend alone or even chiefly on the touch spots, but, as has been pointed out, on the muscle sense. Within the range of pressures, the effects of which are purely cutaneous, it may be asked how are intensities recognized?

Due to the physical situation above outlined, the extent of the deformation increases with the force of the contact, and the intensity of the sensation is largely dependent on the number of receptors affected. This is shown by the fact that to perceive variations, the changes in pressure must be far greater in regions of sparse touch

spots than where they are numerous. On spots so well isolated that spreading is excluded it is possible, however, to perceive variations in pressure, although the changes must be four or five times those required in regions where the spots are plentiful. The number of steps that can be recognized under this condition is so small, apparently but three or four, that it is probable that they represent the successive involvement of the several nerve fibers reaching each receptor.

Localization.—One feature of touch deserves special attention. It is possible to locate the object stimulating the skin with a high degree of accuracy, an accuracy exceeded only in the case of the retina (page 661), with which, indeed, the skin shows many points of similarity. *Space perception* or *localization* closely associated with the sensations from many receptors has already been mentioned (page 494), and its nature may well be illustrated by the situation in the skin. Here the simplest form of space perception would be that arising from the stimulation of the unmoved skin, that is, the skin of some part of the body while at rest. The existence of the ability to localize may be shown and its accuracy tested in two ways. We may touch the skin of a blindfolded person and require him to point out, describe or name the place touched, or we may touch his skin simultaneously with two points, using, for example, a compass, and determine how far the points must be separated to be felt as two (two-point threshold). Upon what does the power of localization depend?

Two touches of the same intensity and duration in two well-separated places presumably give rise to two similar nerve impulses differing only in the anatomical position and relation of the fibers involved, yet the centrally aroused nervous activities differ in some way, since the person can point to or name the place touched in each case, or, to word it differently, each touch leads to a different and appropriate reaction. A little observation will show that movement is an important feature in the perception of position. The natural response of most persons is to touch or point out the spot stimulated. They may instead describe the place, but if pressed for more detail will usually end by asserting that it was "right there" and pointing with a forefinger. It is clear, from the readiness with which the appropriate movement is carried out, that the impulse from the skin arouses in the brain a muscle sense memory of previous movements.

The stimulation of an unmoved skin is the exceptional case, most contacts come from movements of the hand, and to obtain the clearest idea of an object we "feel" of it, that is, move our finger-tips over it and trace its outlines. In this way touch and muscle sense are simultaneously aroused and always in certain definite relations. A particular movement of the arm shifts the contact of an object

from a particular point on the skin to a second point, the relation of which to the first is always the same for the same movement. An object in contact with a particular point of the skin is judged to be now in this and now that position in the outside world, depending on the position of the arm. In a similar manner the sensations from touch and from the muscles are linked with those from sight.

Since there is no evidence of qualitative differences in the impulses from different points of the skin, we must assume, as in the case of the modal senses (page 485), that differences in the central connections determine what muscle sense or visual memories are aroused by an impulse from a particular region of the skin. These differences of quality dependent upon central connection furnish the ground work upon which it is possible to build up with the sensations from other receptors a consistent spatial perception, so that each point touched gives its own quality or *local sign*.

Experience builds up by many repetitions over a long period a working agreement between touch, muscle sense, vision and possibly other senses, with the result that a touch to the skin evokes the proper percept of position, that is, calls up memories of sight and movement appropriate to the position in space of the object touching the skin.

A region in which conditions hinder such development of space perception is furnished by the mouth, which is relatively inaccessible to both the hand and the eye. Although the tongue has an unusually delicate sense of touch, and can detect minute irregularities in the surface of a tooth and distinguish this tooth from its fellows, we often make gross errors when we attempt to touch the roughened tooth with the finger. This lack of agreement undoubtedly comes from the fact that the tongue, hand and eye seldom receive simultaneous stimuli from an object within the mouth.

An interesting example of an extension of this process of perceptual development is furnished by the so-called *projection of touch*. If an object touches the finger-nail or is held between the teeth, or brushes the hair or comes in contact with some other insensitive portion of the body by which the force may be transmitted to receptors in the skin, the object is correctly located and "felt" at the tip of the insensitive structure. Even an object explored with a probe or a cane held in the hand may be naturally and quite accurately localized. This power of "feeling" with an insensitive part of the body or with an external object arises through simultaneous sense experience, in which the skin and the eye coöperate in essentially the same manner as has just been suggested.

Let us now consider the problem of distinguishing two simultaneous touches. It might be expected that two points, the separate stimulation of which caused differing spatial perceptions, ought each to be correctly located and recognized as two if stimulated

at the same time. If, however, the compass points are placed nearer and nearer together a separation is finally reached at which they cannot be distinguished from a single point. Tested thus, different parts of the skin are found to differ widely in delicacy of touch, as shown in the subjoined table. What physiological condition sets a limit to the perception of twoness? If the two points are so close as to affect the same receptor, no separate recognition could be expected. If placed on adjacent receptors two impulses would be aroused; if both reached the brain would the points be recognized as two?

Average Two-point Thresholds in Different Regions of the Skin.

Region.	Mm.
Tip of tongue	1
Volar surface terminal phalanx of finger	2
Red surface of lip	4
Palm	11
Forehead	22
Back of hand	32
Forearm and leg	41
Upper arm, thigh and middle of back	67

The values, expressed to the nearest mm., are from Weber.

The following considerations will show that the perception of two objects from the stimulation of adjacent receptors is not a physiological possibility. If *a*, *b*, *c* and *d*, Fig. 61, represent

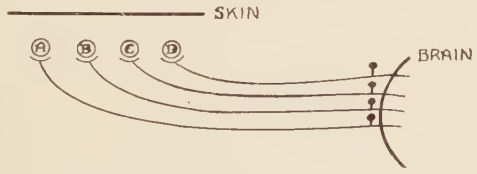

Fig. 61.—Diagram of cutaneous receptors with central connections.

separate receptors with separate nerve fibers to the brain, it is clear that the physiological activities would be identical whether one point stimulated *a* and another *b* or a single larger object stimulated both. Since the physiological consequences are the same, the two happenings cannot become linked with different percepts, but must remain subjectively the same. If adjacent receptors gave rise to separate sensations of touch, no surface would seem continuous and a pane of glass would feel to the hand like the back of a porcupine. The results are different, however, when *a* and *c* or *a* and *d* are stimulated simultaneously. Here the impulses generated by two objects, one on *a* and the other on *c*, cannot be duplicated by a single larger object which would of necessity stimulate the intervening *b*. It is, therefore, possible to

link the two physiologically different effects with two different percepts, activity of *a* and *c* signifying "two" and *a*, *b* and *c* signifying "one." The recognition of two separate objects requires the presence of a stimulable but unstimulated intervening receptor. This picture is, of course, simplified from the actual conditions. If applied to the ordinary "compass test" we must remember that as used these points nearly always exert enough pressure to stimulate the muscle below and that through these muscles we are also able to recognize double touches, even if the skin is insensitive. If the pressures are light enough to affect the skin only, each point still causes an area of deformation involving not one but a group of receptors. If, as seems probable, two or more receptors are reached by branches of a single nerve fiber our conception must be correspondingly altered. This discussion will apply with equal force to any surface supplied with a number of similar receptors, for example, the retina.

Reflexes.—The touch spots differ from the remaining cutaneous receptors, in that, while they lead to important sensations and the most accurate spatial perceptions, they seldom evoke conspicuous or easily recognized reflexes.

CUTANEOUS PAIN.

We have already pointed out differences between touch and pain which entitle pain to a separate status. Recalling that for the present we are dealing with cutaneous pain only, a more systematic treatment may now be attempted.

Pain is unique among the senses, in having a variety of customary stimuli. Its receptors (sometimes called *nociceptors*) are least specialized in the direction of selective sensitivity (page 474) and respond not only to strong mechanical stimuli but also to extremes of temperature (above about 45° C. and below about 10° C.) to strong acids or alkalies and the like. Although the pain receptors are primitive in lacking either the marked selective action or the increased sensitivity of most other receptors, this very condition gives to the effective stimuli a common physiological significance; diverse but intense forces all tend to harm the skin.

For exploration of the skin von Frey hairs of greater stiffness than those used for touch or bristles that may be sharpened to reduce the area acting upon the skin are most convenient. Because of their abundance the enumeration of pain spots is much more difficult than of touch, warmth or cold spots. Competent workers have found between 100 and 150 per sq. cm. in various regions, from which the number for the entire skin may be estimated at from 2,000,000 to 3,000,000.

The receptors for pain are apparently the "free" intra-epithelial

nerve endings. These alone are present in the center of the cornea where any effective stimulus causes pain. In the skin they are abundant, as is required by the immense number of pain spots, and superficial in position, thus agreeing with the physiological evidence that pain receptors lie nearer the surface than those for touch, warmth or cold. How these endings transmute the diverse effective stimuli into nerve impulses is not known. As stated, the stimuli presage harm; in general, the threshold is such as may allow protective reflexes to prevent actual injury, thus the degree of heat or cold that will cause pain is less than that injuring the tissues and a needle will cause pain before it pierces the skin. In structures unusually delicate or important the threshold for mechanical stimulation is very low, this is true of the ear drum and particularly of the cornea, where the contact of even a wisp of cotton is painful. Though histologically very simple, these so-called "free" endings show terminal knob-like swellings and seem often associated with modified epithelial cells; this fact, together with the physiological findings, that their threshold though high is yet lower than that of

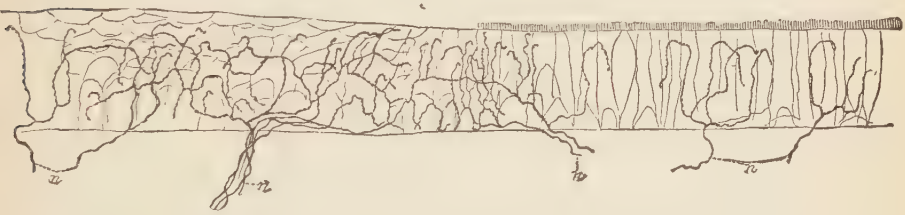

FIG. 62.—Intra-epithelial nerve endings in larynx; Golgi method. (Retzius.) (From Schäfer's "Essentials of Histology," by permission of the author.)

a bare nerve fiber, indicates that they are true receptors. It has been suggested by von Frey that the mechanism is in the last analysis a physico-chemical one and that, as in his view of touch, pressure causes changes in concentration about the endings.

Physiologically of the most significance are the reflexes initiated by this sense. As has been stated, they constitute a distinct class, the protective reflexes (page 477). Not only are they clearly adaptive, removing the insulted skin from the source of injury or the source of injury from the skin, but they are *prepotent*, that is, have the right of way and interrupt other reflexes that may be in progress. The sensation of pain is of a nature to reinforce the adaptive effect of the reflexes. It makes a deep impress in memory so that not only painful happenings but even initially indifferent sensations if once linked with pain are afterward avoided. In this way the protective reflexes which normally anticipate by a small margin, or even follow some degree of injury, may come safely to precede it from being initiated by some distance receptor, which

responds far sooner to the threatening object than can any of the cutaneous receptors. In addition, pain, particularly if severe, sets in action a chain of activities called by Cannon, who carefully investigated it, the emergency reaction (page 735). First through the stimulation of the thoraco-lumbar autonomic system and then through the secretion of adrenin there is placed at the disposal of the neuromuscular system for immediate flight or fight all the resources of the organism. Fatigue, if existent, is wiped out, other activities are suspended and the blood is flooded with sugar for consumption by the muscles—a most surprising series of adaptive reactions. Sherrington has well said of pain that "In the struggle for existence it is doubtless one of the most potent weapons Nature has devised."

PAIN IN DEEPER TISSUES.

Intense stimuli applied to tissues other than the skin may cause pain. This differs in many ways from cutaneous pain, it is less well known and, concerning many features, there have been and are great differences of opinion. For this reason no extended treatment will be attempted, though certain important features deserve comment.

Pain may arise under certain conditions in the majority of the organs of the body. The tissues differ widely both in their sensitivity to pain and in the nature of the effective stimulus. Pricking, cutting and other harmful mechanical stimuli and thermal stimuli in the form of extreme temperatures, all of which are so potent for the skin, evoke pain from certain internal structures, notably the parietal pleuræ and peritoneum, the dura mater, the periosteum covering the bones, and the trachea, but many other tissues may be cut or burned without sensation or the appearance of reflexes. Yet from the intestine or ureters, for instance, which do not resent these forms of insult, may arise the well-known pain of colic or the pain caused by the passage of a renal calculus, said to be the "most severe to which man is heir." This apparent contradiction comes from confusion regarding the nature of the effective or customary stimulus. The internal organs are well shielded from contact with thorns and stones and from the extremes of heat and cold. It is notable that among the few internal structures sensitive to these stimuli are the membranes lining the thorax, the abdomen and the skull; these lie near the exterior and must suffer injury before the deeper organs are reached. For the more sheltered organs mechanical stimuli could have little significance; their effective stimuli are of a different type. In the hollow viscera this is usually distention. Thus the passage of a calculus through the ureter, distending it beyond its normal limits and accompanied by unusual peristaltic contraction, is painful; the violent peristalsis of colic, particularly

when there is some obstruction and the contents develop abnormal tensions in the walls, produces pain. In some organs, as the liver and spleen, pain does not occur except in a diseased condition, and then it is claimed by authorities always to be associated with swelling and to be produced by the tension developed in the relatively inextensible capsule. In other cases we are ignorant of the mechanism of pain production. In some organs pain perhaps never occurs; possible examples are furnished by the lungs (if the parietal pleura and bronchial tree are not affected) and the brain (if the dura, the roots of the sensory nerves and certain parts of the thalamus are not involved).

The identity of the pain receptors in deeper tissues is not known. Possibly they are of more than one type; certainly from the nerve endings known to be present in these organs they must be simple in structure.

The reflexes produced are naturally of interest and present certain difficulties. The reflexes from the cutaneous pain receptors are all clearly and directly protective. This is also true of some of the pains from deeper organs, but there are many cases where the utility is not clear. The pain of the passage of a calculus through the ureter may lead a man to consult a physician, but its usefulness to an animal seems problematical. When, however, all types of evidence are collected many adaptive reflexes are found. Everyone is acquainted with the fact that pain in a joint or a muscle leads, if severe, to immobilization of the affected limb, thus preventing the irritation of the diseased or injured part by movement. If less severe or more limited the painful movement alone may be avoided, as in limping. In pleurisy there is a marked change in respiration, which becomes shallow, thus minimizing the movement between visceral and parietal pleuræ and reducing the pain and injury. In disease of the abdominal viscera in which pressure is painful the lightest touch on the abdominal walls will cause protective reflexes of the abdominal muscles, which contract and shield the sensitive viscus from further injury. These visceromotor reflexes are well known to the examining physician, and have been experimentally studied in animals so that the main features of the paths are known.

Sensations.—The sensations of pain from the internal organs often differ in character and have received descriptive names, such as "throbbing," "stabbing," "gnawing pains" and the like. That qualitative differences in pain may exist is possible; many of the differences indicated by such terms are, however, dependent on other sensations or on differences in duration, intensity or some other feature; for example, a "throbbing pain" us one in which each pulse-beat causes an increase of the pain. There is, in the present state of our knowledge, nothing to be gained by considering pain to be of more than one character.

Cutaneous pain is less accurately localized than other skin sensations; internal pains are even more vaguely localized. Some are merely felt as "within;" often the location is based on other clues. A "stomach ache" is located more in accordance with the person's idea of the position of the stomach (often erroneous) than from the sensation, the verbal clue prevailing in spite of the fact that the "stomach ache" arises in the intestine and not in the stomach. The poor development of localization is probably due in part to the sparse innervation, the few paths precluding under any conditions an elaborate space representation, and in part to the nature of the stimulation. It is often not association with an "object" and so could not be simultaneously presented to other senses, or, if due to an object (as a calculus in the ureter), this object does not stimulate other receptors.

Associated with the vague localization are the curious cases of mislocation—*referred pains*. Often the pain is localized in the skin, not over the diseased viscus but at some, often remote, distance. Thus, diseases of the gall-bladder cause pain in the right scapular region. This misreference is not at random, but so regular that it is often possible to identify the internal organ by pain or tenderness in a particular region of healthy skin. Anatomical investigations show this relation between the skin and the viscus in which the impulse arises; the afferent fibers passing through the sympathetic from the viscus enter the cord at the same level as the afferent fibers from the "painful" skin. Whether there is an actual anatomical connection between these fibers by which impulses from the viscus may "spill over" into the skin pathways, or whether it is merely an exaggeration of a general tendency known to psychologists by which a sensation from a region with poor localization tends to be referred to a region with better localization, is not clear.

Summary.

The *exteroceptors* stimulated by objects outside the body may be divided into two groups those more sensitive receptors responding to objects at a distance (*distance receptors*) and those less sensitive forms responding only to objects in contact with the body (*contact receptors*). The present chapter deals with those contact receptors found in the skin (*cutaneous receptors*). The cutaneous receptors have been shown by selective stimulation and by the facts of cord conduction to be of at least *four* and possibly *six types* -*warmth* and *cold* (temperature) receptors, *touch*, *pain* and perhaps *tickle* and *vibration*.

The cold receptors (probably end bulbs of Krause) underlie *cold spots*, from which sensations of cold are obtained. These number 12 or 13 per square centimeter and total 250,000 for the entire

body. *Warmth* receptors (not identified) underlie warmth spots numbering 1 to 2 per square centimeters and totaling 30,000. These receptors lie near the surface of the skin through which passes to the usually colder air from 1800 to 3000 calories of heat per day. A marked temperature gradient is found from 6 to 7 cm. within the skin to about the same distance in the air outside. A rise or fall of the external temperature causes a readjustment of this gradient and a rise or fall of the receptor temperature. *A change of temperature exceeding a certain rate* (0.15° to 0.2° C. per minute) *stimulates* the receptors, giving rise to a sensation of warmth or cold and to reflexes.

Exposure to a temperature within the range usually experienced soon leads to an equilibrium in the receptors and no further sensations are felt. This adjustment does not impair the capacity of the receptors to respond to a further change, and hence is a true *adaptation*. When adapted to a certain air temperature objects having an equal heat receptivity cause no change of the receptor temperature and, therefore, no sensation, and are said to be *indifferent*. The *indifferent temperature* is most commonly determined with *water*; other substances give characteristic indifferent temperatures dependent upon their physical properties. The *range of adaptation* varies in different parts of the body, being greatest in the finger (10° to 45° C.). The limits are apparently set by the points at which the pain receptors are involved.

When the external temperature is raised above that felt as indifferent the sensation of warmth increases in *intensity*, due apparently to the involvement of more and more *warmth spots*. With further rise the *cold spots* are stimulated, giving a sensory fusion called *hot*, and finally the *pain spots* are affected, giving *burning hot*. With lowered temperatures the warmth spots are apparently not stimulated, although the *pain spots* are, at or below 10° C.

The temperature receptors from their position and mode of action are admirably adapted to *indicate changes in the temperature relation between an organism and its surroundings*, and their chief biological importance lies in their contribution to the process of *temperature regulation*.

Contact of objects with the skin causes changed pressure relations at the depth of the receptors and stimulation of the *touch* and *pain* receptors, which differ in a number of characteristics. *Touch spots* number from 9 to over 100, averaging about 25 per square centimeter and total about *half a million*. The receptors are of two kinds, *tactile corpuscles* on the palms of the hands and the soles of the feet and the *nerve rings of the hair follicles*. *An increase or decrease of pressure above a certain rate is the effective stimulus*. *Adaptation* is a feature of touch, although less marked than in temperature. *Intensity* of touch sensation apparently

depends on the *number of touch spots stimulated,* since intensity is poorly distinguished in regions of sparse spots.

Stimuli affecting touch are very accurately *localized.* The power of discriminating between neighboring spots as tested by the *two-point threshold* varies in different parts of the skin. Few or no *reflexes* arise from touch.

Pain spots in the skin are very abundant, numbering between 100 and 150 per square centimeter, with a total of 2,000,000 to 3,000,000. The receptors are apparently the *free intra-epithelial nerve endings.* They represent a primitive type of receptor with a *high threshold* and *small selective sensitivity,* this responding to many forms of stimuli. These varied and intense stimuli have a common *biological significance—impending injury*—and hence the prominent *protective reflexes* are extremely important to the animal.

The mechanism of pain in other tissues than the skin is not well known. Examples of useful reflexes are the fixing of painful joints and the guarding of painfully diseased viscera by defensive contraction of the abdominal walls. Cutaneous pain is less strongly localized than touch; visceral pains are still more vague in location and in some cases are "felt" in more or less distant areas of skin. These *referred pains* are so regular in occurrence as to aid the physician in diagnosis, but their mechanism is not understood, although it is known that the afferent fibers from the viscus in question enter the cord in the same segment as those for the skin where pain is felt.

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CHAPTER XXXIII.

TASTE AND SMELL.

Taste and smell present resemblances and differences that properly understood throw much light on the nature and functions of receptors. In man the stimuli for both are chemical. A distinction is often made that taste is stimulated by substances dissolved in the fluids of the mouth, whereas smell is stimulated by air-borne gases or finely divided solids. Comparative physiology shows, however, that this distinction is far less significant than that of their difference in delicacy. Parker has shown that few substances actually stimulate both; when this occurs, as with ethyl alcohol, smell is some twenty-four thousand times the more sensitive.

Responses to chemical stimuli are found in very simple organisms, but the receptors are not well known. In the vertebrates, however, the receptors have been carefully studied; in the fish, for example, they exhibit a threefold differentiation.

Taste buds are present not only in the mouth but in many parts of the skin of the body; vastly more sensitive olfactory organs limited to pits adjacent to or communicating with the mouth are present, and, in addition, a less sensitive and widely distributed common chemical sense is to be found. This latter is shown to be distinct from taste which has, in part, the same distribution over the body surface, by the fact that it is unaffected by section of the facial nerve supplying the taste buds of the skin. That it is also distinct from touch and pain, with which its receptors show the closest resemblance, is indicated by the response of narcotized animals in which the withdrawal reflex to strong mechanical stimuli is absent, but which react to weak acids.

In man smell retains its localized position and outstanding delicacy. Taste and common chemical sense are both absent from the skin which, specialized to resist the loss of water to the air, no longer affords the moist condition needed for these receptors.

Taste is restricted to the tongue and a few closely adjacent structures, common chemical sense to sheltered mucous surfaces where the requisite moisture is present. The distribution of the common chemical sense is thus distinctly more extensive than taste, since it is found in the mucous surfaces of both the mouth and the nose, the conjunctiva of the eye and other mucous surfaces.

Ammonia vapor acts upon the common chemical sense in regions of the nose or in the eye far removed from either the olfactory or gustatory receptors, and there is other proof that in man it represents a distinct sense less sensitive than taste. Its sensations are characteristic but are not as conspicuous as those of the other chemical senses. The reflexes which it initiates are protective, the "watering" of the eye, coughing, sneezing and choking; in this it resembles pain as do its sensations.

We may look upon taste in man as a remnant of a general contact extereoceptor which, from its position at the entrance to the alimentary canal, has come to have so intimate a relation to visceral activities (secretion of saliva) that many would classify it as a visceroceptor. Smell has retained a high measure of its sensitivity and in contrast with the condition in the fish is restricted almost wholly to substances not tasted. Because of its great delicacy it functions as an important distance receptor.

TASTE.

Receptors. We will first consider taste. Its receptors are the taste buds, or, more exactly, the gustatory cells within the taste buds. These are found on the tongue, epiglottis and certain parts

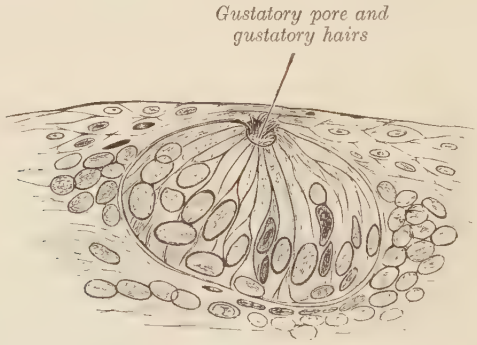

FIG. 63.—Taste-bud, highly magnified. (Gray's Anatomy.)

of the pharynx and are innervated from three sources. The nerve fibers are not continuous with the gustatory cells but end around and in some sort of intimate relation to them, since after section of the nerve the taste buds soon degenerate and disappear. The few taste buds on the epiglottis and some on the most posterior part of the tongue receive fibers from the vagus, those on the posterior third of the tongue from the glossopharyngeal and those on the anterior two-thirds from the lingual branch of the trigeminal. These latter fibers, however, do not enter the brain through the trigeminal root but are derived through the chordi tympani from

the facial and enter the brain through the root of the facial or possibly of the glossopharyngeal. (See Fig. 127, page 709.)

Stimulus.—The stimulus is a change in the concentration of a soluble compound of suitable character. Although many substances stimulate taste, the sensations fall into a few categories. Four of these are generally recognized—*sour*, *salty*, *bitter* and *sweet;* two others, *alkaline* and *metallic*, have been claimed by some workers but may involve other receptors than those of taste.

Sour.—The sour taste is associated with acids and, since these have in common only the hydrogen ion, this is generally considered to be the chemical basis of the sour taste. This view is supported by other evidence. Hydrochloric acid tastes sour at a concentration (0.0025 molar) at which the chlorine ions as tested by solutions of sodium chloride are entirely tasteless. The sour taste is depend-

FIG. 64.—Cells from taste-bud of rabbit (Engelmann); *a*, four gustatory cells; *b*, one sustentacular cell and two gustatory cells in position; *c*, sustentacular cells. (From Schäfer's "Essentials of Histology," by permission of the author.)

ent upon the presence of hydrogen ions and in general the intensity or sourness corresponds to the hydrogen-ion concentration, although the correspondence is far from exact. The organic acids such as acetic are far more sour than mineral acids, such as hydrochloric, of the same pH, a fact apparently dependent upon the penetrating power of the organic acid molecules which presumably enter the gustatory cells. This is in accord with the general finding that organic acids have a greater physiological efficiency than do inorganic, a fact that Loeb attributed to the greater power of penetration of the undissociated molecules of the fatty acids.

Salty.—The chemical basis of the other qualities are less clear. The salty taste is apparently dependent upon the chlorine ions furnished by a variety of chlorides which have the same taste, and less characteristically upon the bromine and iodine ions of various bromides and iodides.

Bitter.—The bitter taste is characteristic of most alkaloids, but also of some quite unrelated substances, such as magnesium sulphate,

dextro-mannose, certain of the vegetable glucosides, as amygdalin, and picric acid. The alkaloids, such as quinine and particularly strychnine, are intensely bitter, 0.000005 gm. of the latter in 5 ml. of water giving a pronounced taste. In the face of this diversity of chemical stimuli the attempts to explain the mechanism seem quite inadequate.

Sweet.—The sweet taste is associated in our minds with the sugars, and it is notable that fish do not react to sugar, an element normally absent from their environment. Although the sugars are sweet, the related substances, starch and glycogen, are tasteless. Dextro-mannose is bitter whereas its stereoisomer dextro-glucose is sweet. Dextro-asparagine is sweet and levo-asparagine is tasteless. Saccharine, about five hundred times as sweet as sugar, is quite unrelated to it. Parabamic acid, chloroform, the salts of beryllium and the familiar lead acetate are sweet.

From this brief survey we can see that, although taste is a chemical sense and its physiology must in time find a rational basis in its chemistry, more knowledge is required before this is possible.

The Physiological Basis of the Taste Qualities. The four qualities of taste, sour, salty, bitter and sweet, are so distinct as to be considered modal senses by some workers. This raises the question of whether there are separate receptors for these qualities. This problem is, however, complicated on the experimental side by the difficulty of restricting the liquid stimuli to definite small areas and on the anatomical side by uncertainty as to what is the receptor unit. Taste buds are found in certain types of tongue papillæ, the fungiform, foliate and vallate, but not the filiform. The number of buds is from 3 to 8 in the fungiform and from 33 to 508 in the vallate. Each taste bud may contain from 3 to 10 active gustatory cells. If individual nerve fibers do not supply more than one gustatory cell, the cell might be considered the unit, but the separate stimulation of such a unit is experimentally impossible.

The experimental facts are these. The power of perceiving the different tastes is not uniformly distributed, thus bitter is more readily tasted at the base of the tongue than at the tip, whereas sour is more marked at the sides, an arrangement suggesting separate receptors which differ in number in different regions. A careful stimulation of individual fungiform papillæ has given interesting results. Papillæ were found responding exclusively to sour, to salty and to sweet stimuli, but none to bitter alone. The failure to find papillæ giving solely bitter sensations may be related to the fact that bitter is better marked at the base of the tongue, whereas the fungiform papillæ tested are in the anterior part. Papillæ were found that failed to respond to any of the four tastes, while some responded to two, some to three and some to all four types of stimuli. When we consider that each fungiform papilla contains

from 9 to 80 active gustatory cells, so that the chance association of only one type of cell is very small, these results can only have one interpretation; that the unit is the gustatory cell or a small group of cells supplied by one nerve fiber and that these units are of four types, each responding exclusively to one kind of stimulus with one sensation.

Accessory Factors.—Certain non-chemical factors are also involved in the activity of the taste receptors. Thus a temperature approximating that of the body is most favorable to the production of taste sensations. Movements of the tongue, as in "smacking the lips," increase the sensitivity presumably by spreading the solution over a larger area and facilitating its entrance into the taste buds.

Reaction Time.—Taste sensations develop slowly, probably because of the dilution of the test solution by the natural fluids of the mouth and its slow entrance through the narrow pore into the taste bud. The reaction time is, therefore, long, sometimes exceeding a second; this differs for the four qualities of taste and for different regions of the tongue.

Intensity of Sensations. No experimental data are at hand bearing on the mechanism of sensory intensity. If the unit is the gustatory cell, the number of these stimulated probably determines the intensity of the sensation.

Reflexes.—The reflexes initiated by taste are chiefly visceral; it stands last among the receptors that are affected by food before it passes from the region of voluntary control into the alimentary canal. Secretion of saliva is a prominent reflex, but other reflexes of a somatic type, such as sucking or licking with the tongue, follow the stimulation, chiefly from sweet.

SMELL.

Receptors. The olfactory receptors are located in the upper part of the nasal cavity in an area of about 500 sq. mm. on either side, partly on the septum and partly on the superior concha. The olfactory epithelium contains three types of cells, the short basal cells and two elongated forms, the larger sustentacular or supporting and the more slender *olfactory cells*. Each of these last cells ends on the free surface of the epithelium in a small group (5 to 8) of delicate protoplasmic projections or *olfactory hairs*, often destroyed in histological preparations. The inner end narrows to form the olfactory nerve fiber which ultimately enters the olfactory bulb of the brain. Structurally the olfactory cells are unique as the only receptors in the human body representing the primitive type of receptor found in many invertebrates in which the cell body of the afferent neuron lies in the epithelium. Since the glands of Bowman are confined to the olfactory region, it is probable that they are an

accessory feature of importance in maintaining a proper environment for the olfactory hairs.

The extent of the olfactory epithelium in man is much less than in some other mammals, such as the dog, in which smell is much more delicate. Even a shark of less than one-half the length of a man and less than one-fifteenth the weight has an olfactory surface between four and five times as extensive.

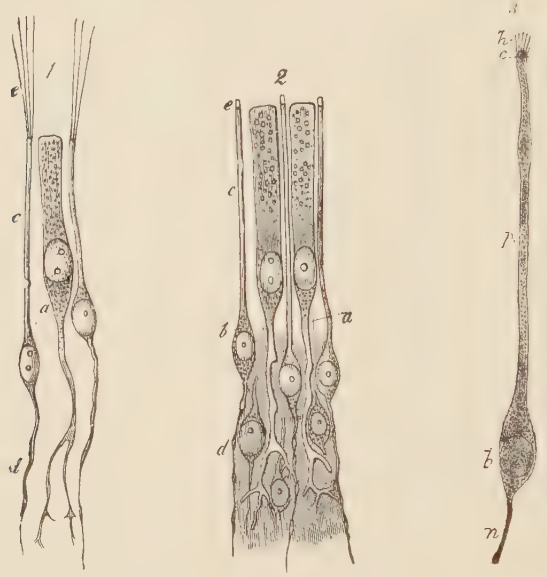

FIG. 65.—Olfactory and supporting cells. 1, of the frog; 2 and 3, of man. 1, of the frog and 2, of man (Schultze). *a*, supporting cell; *b*, *c*, *d*, olfactory cell; *e*, hairs. 3, of man (V. Brunn), *h*, hairs; *c*, free border of cell; *n*, nerve fiber. (From Schäfer's "Essentials of Histology" by permission of the author.)

Stimulus.—The stimulus for smell in terrestrial mammals consists of changes in concentration of certain substances in the air over the olfactory epithelium. Although both are chemical senses, smell and taste seldom respond to the same stimuli, and in man the substances tasted are usually not smelled and those smelled are usually not tasted. Although clearly a chemical sense, the chemical peculiarities of the stimulating substances are by no means clear. Physically the odorous substance, whether it reaches the nasal cavity in a gaseous or in a finely divided solid form, must be in solution in water when it affects the olfactory hairs, since these lie in the watery mucous furnished by Bowman's glands. Evidence is accumulating that odorous substances are more soluble in oil than in water and that the olfactory hairs are lipoid in character. If this is true the stimulating substance would first go into solution

in the mucous and thence into solution in the hairs. If parts of the hairs reach the air, direct solution in the hair is possible, but in view of the short and delicate form of the hair and the olfaction of water-living forms, like fish, this seems less probable. Further than this fact of lipoid solubility, the data on the physical and chemical nature of odorous substances are too fragmentary to admit of significant generalizations.

Classification of Odors.—Unlike tastes, odors cannot readily be grouped into a few categories, a fact indicated by the absence of names for classes of odors corresponding to sour, bitter and the like. Various classifications of odors have been proposed. In spite of the fact that in certain groups, as the alcohols, there is a parallelism between the chemical composition and the smell, odors are on the whole strikingly individual and the classifications artificial and unconvincing. A satisfactory classification must await further knowledge.

A mechanism for olfactory quality presents grave difficulties. We may assume separate receptors which in the absence of clear classes must be almost impossibly numerous, or we may assume fusions between receptors of a few types for which there is no clear evidence. Neither possibility has much to recommend it.

How Odorous Substances Reach the Receptors.—We have stated that the stimulus is a change in the concentration of an odorous substance over the olfactory epithelium. In order to see how this change occurs we must consider the air currents in the nasal cavity. With each inspiration the air passes through the nasal cavity on its way to the lungs, but its course normally lies lower than the region of the olfactory epithelium. The course of the expired air is essentially the same. The exact course of the inspired air varies with the velocity of the current. Since the nostril is directed upward, a sharp inspiratory movement causes the air current to rise higher, thus "sniffing" brings the odor more directly to the olfactory epithelium. Slight eddies and diffusion probably serve to bring the odorous material to the olfactory receptors from the general inspiratory current in quiet breathing.

If the change in concentration is rapid enough it constitutes a stimulus. If the view expressed above is correct, and the substance goes into solution first in the mucous and then in the olfactory hairs, stimulation would ultimately depend upon changes in concentration in the hairs. All of these processes go on fairly rapidly probably because of the small distances involved. Although the reaction time of smell cannot be measured with great accuracy, the time from the presentation of the odor to the nose until it is smelled is only two- to eight-tenths second, a time which must include both the movement of the air to the olfactory epithelium and the penetration of the odorous substance into the hair.

Adaptation.—That a change of concentration is essential is shown by the fact that if the air breathed contains a constant amount of an odorous substance it soon ceases to stimulate. Even as pronounced an odor as camphor is not detected after five to seven minutes. This is, of course, in agreement with our experience, that we soon get "used to" a smell and no longer notice it. Although commonly referred to as fatigue, it is really a case of adaptation. This is well shown by an experiment of Zwaardemaker's. If a person breathes air with a constant content of an odorous substance such as rubber, and the threshold of this substance is determined at intervals, it will be found to rise steadily with the exposure, as shown in Fig. 66. The receptors are not incapable of function, but the substance must be presented in higher and higher concentrations.

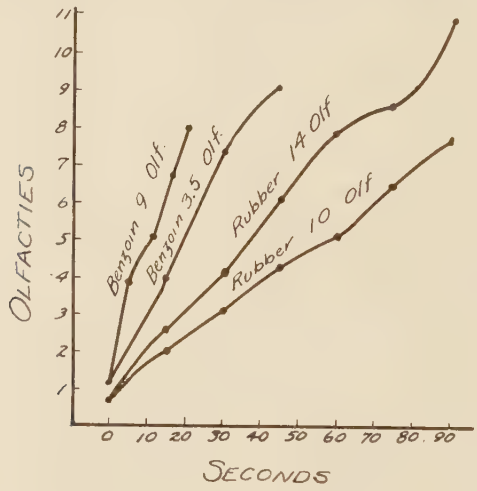

FIG. 66.—Adaptation in smell (data from Zwaardemaker). When exposed to a continuous odor of the intensity indicated on the curve, the successive thresholds at fifteen-second intervals are shown by the points.

The process of adaptation is here probably a relatively simple one. Material from the air enters the mucous and thence the olfactory hairs, and if the substance is indefinitely soluble in oil, as some odorous substances are known to be, the amount in solution will be directly proportional to the time of exposure. At any given time, then, a concentration higher than that existing in the hairs will have to be presented in order that a change in concentration may take place in the hairs.

Threshold.—Bearing in mind that the stimulus should be measured as a change from an existing level and that it should occur above a certain minimum rate, we may consider the threshold of smell. The minute amounts of certain substances that may be

detected is remarkable. Thus chloroform may be smelled at a concentration of 3.3 mg. per liter of air; oil of peppermint, at 0.2 mg.; artificial musk (trinitro-isobutyltoluene), at the almost incredible dilution of 0.00004 mg. per liter. If we estimate that 50 ml. is the amount of air necessary for olfaction, the amount of musk passing through the nose, of which but a part could reach the olfactory hairs, would be only 0.000002 mg.

Since many mammals, such as the dog and deer, are far keener of smell than man, the amount required to stimulate their olfactory receptors must be inconceivably small.

Neutralizing and Combining Odors.—Regarding the sensations, the unsatisfactory state of attempted classifications has been noted. Some other facts are of interest. Certain odors if combined in the proper proportion neutralize each other, so that no sensation is produced; an example is rubber and paraffin. This is true even when one odor is supplied to one nostril and the other to the other, so that it does not come from chemical interaction between the stimuli. In other cases certain pairs of odors give rise to a sensation different from that produced by either alone.

Location of Odors. Man's power of localizing odors is very slight. By moving about we may be able to detect differences of intensity, and so finally reach the source of the odor, but this is all. In some other vertebrates, however, a true binolfactory location of stimuli occurs. This has been shown experimentally for the dogfish which, if one nostril is plugged, turns to the opposite side, that is, to the side receiving the stronger stimulus. This would lead the swimming animal to the food giving off the odor.

Relation to Taste.—The sensations, as already stated, bear an intimate relation to taste. Normally food entering the mouth may be smelled as it passes the adjacent nostrils; odors from the food within the mouth or passing through the pharynx in swallowing may also reach the olfactory membrane through the posterior choanæ. Since this so readily occurs there is much confusion in the mind of the average person as to what is tasted and what is smelled. Things in the mouth are assumed to be tasted, and that they appeal to smell is not recognized until smell is artificially excluded. It is possible to do this by holding the nose and preventing odorous material from reaching the olfactory membrane on air currents through the nasal cavity. When this is done it is a surprise to learn that the characteristic flavors of bits of apple, carrot or even onion are lost, and that taste alone will not enable us to distinguish them. Thus a person complains that a cold "makes food lose its taste" when taste is unaffected, but smell has been impaired by the "stopping of the nose."

Reflexes.—Reflexes from material in the inspired air may be of two kinds—those from irritants acting upon the common chemical

sense and those from true olfaction. The reflexes from the former are protective, as sneezing, and represent a simple consummatory form. The olfactory responses are, like those of the other distance receptors, mostly of the anticipatory type, as the finding of food, detection of friends and of enemies. Phylogenetically, smell was early differentiated from taste and is found in a highly developed state, for example, in fish. Since it was the first of the distance receptors it has left a remarkable impress on the brain. Thus in the dogfish approximately one-third of the brain represents primary olfactory centers and correlation centers in which smell is dominant. Even in man, where smell is subordinated to sight and hearing, odors have an affective tone and call up memories in a more striking manner than any other receptor.

Summary.

There are present in man three forms of chemical receptors: *Common chemical receptors* of low sensitivity, found in the mucous lining of the mouth, nose, eye and the like; *gustatory cells* of higher sensitivity, found in characteristic taste buds on the tongue and some adjacent parts of the mouth and pharynx; *olfactory cells* of extremely high sensitivity, found in the olfactory epithelium of the nasal cavity.

Taste buds are present in the *fungiform, foliate* and *vallate* but not in the filiform papillæ of the tongue. Nerve fibers from the *glossopharyngeal* and from the *chorda tympani* through the *lingual branch* of the *trigeminal* end about, but not in continuity with, the *gustatory cells*. The *stimulus for taste* is a *change in the concentration of a soluble compound of suitable nature*. All sensations can be grouped in a few categories—*sour, salty, bitter, sweet* and possibly alkaline and metallic. The *sour taste* is apparently due to hydrogen ions, *salty* to the *chlorine* or *bromine* or *iodine ions* of various salts containing these; the stimuli for bitter and sweet form less well-marked chemical groups; *bitter* is produced characteristically by *alkaloids*, such as *quinine* and *strychnine*, and *sweet* by *sugars*; both are, however, produced by a number of compounds unrelated to either group.

From selective stimulation of fungiform papillæ it appears that the *four sensations* come from *four types* of *gustatory cells*. The *reaction time of taste is long*, sometimes exceeding a second. The physiological mechanism of intensity is not known. The *reflexes are chiefly but not wholly visceral;* secretion of saliva is prominent.

The *receptors for smell* are the *olfactory cells*. The distal end of the cell bears a small group of delicate *olfactory hairs*; the deeper end narrows to form a *nerve fiber* of the olfactory nerve which ultimately enters the olfactory bulb. The olfactory cells are the only

receptors in man retaining the primitive form characteristic of various invertebrates in which the cell body lies in the epithelium.

The *stimulus for smell* in terrestrial mammals is a *change in the concentration of certain substances* in the air over the olfactory epithelium. These substances (either gases or finely divided solids) are usually *soluble in both water and oil*, and are thought first to go into *solution in the mucous* covering the olfactory epithelium, and thence into *solution in the olfactory hairs* which are lipoid in nature.

Unlike taste, odors cannot readily be grouped in a few categories and, although various classifications have been proposed, none are particularly significant.

The air in quiet respiration passes through the nasal cavity below the olfactory epithelium which must be reached by eddies or diffusion. In "sniffing" the more rapid inspiratory current rises more directly to the olfactory region. The reaction time is less than that for taste.

Smell shows marked *adaptation*. If air containing a given concentration of an odorous substance is breathed the sensation is not long detected. The concentration in the air, the mucous and the olfactory hairs presumably soon come to an equilibrium, after which a higher concentration in the air will have to be presented to cause a change of concentration in the hairs. The *threshold is extremely low, 0.000002 mg. of artificial musk in 50 ml.* being detectable in man. It is probably much lower in some other mammals.

In man the *power of localizing* an odor is very slight. In some other animals, as the dogfish, a true *binolfactory location* of odors occurs, the fish turning toward the side of the more strongly stimulated nostril.

Smell is intimately associated with taste. Many stimuli thought to be tasted are in reality smelled, the odor from the mouth reaching the olfactory cells through the posterior choanæ.

The reactions initiated by smell are like those of the other distance receptors chiefly of the general anticipatory type and include in animals the finding of food and locomotion away from enemies and toward friends.

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CHAPTER XXXIV.

HEARING.

The power of reacting to mechanical stimuli originating at a distance by means of what Sherrington has called "glorified touch spots" is characteristic of the higher land vertebrates. The longitudinal vibrations of the air are well adapted to transference over long distances with small energy loss, and it is rightly with these that our ideas of hearing are associated. Similar vibrations are conducted through water as well as air, but there is no clear case of any reaction to them among aquatic invertebrates and even in fishes, in which there is evidence of some degree of "hearing," this sense is apparently of negligible importance in their behavior. Hearing as an important sense is limited to terrestrial vertebrates, chiefly mammals and birds, and to some insects. It reaches its highest development in the mammals, which not only react to minute amounts of energy transmitted through the air, but, certainly in man, distinguish between a great variety of sounds, a process requiring an extremely delicate analysis of these stimuli. In accordance with this capacity we find grouped about the essential receptive cells an exquisitely complicated and sensitive set of accessory structures. Hearing plays a correspondingly large part in mammalian behavior, chiefly in relation to other animals. Through it they are warned of their enemies, find their prey and locate their fellows. Special sound-producing mechanisms are found in many animals capable of hearing, and with it some degree of communication which culminates in the speech of man (page 565).

In our treatment of hearing we will consider: (1) The *physical nature of the stimulus, i. e., sound*, and particularly the sounds with which the human ear normally deals; (2) the *structure and action* of those *accessory devices* by which sound is transmitted and transformed in the ear; (3) the *reactions* and *sensations* aroused by the stimulation of the ear; (4) *certain theories* of the action of the *less well-understood mechanisms involved* in the *analysis* of the sounds.

PHYSICAL NATURE OF SOUND.

It is customary to divide physical sounds into two classes—musical sounds, or tones, and non-musical sounds, or noises. While convenient, this division has less significance than might be suspected. Simple pendular air vibrations, although the easiest to

treat experimentally or analyze mathematically, are extremely difficult to produce, requiring in fact special devices for that purpose, and are not ordinarily encountered by the ear. Musical instruments produce complex waves representing the fusion of two to twenty simple rates, standing in definite relations one to another. Such musical tones may also be analyzed, and form the least complicated material usually available for experimental purposes. In proportion as the elements of a complex wave become more numerous and less sustained, and their relation less simple, the sound is felt as more noisy and yields less readily to mathematical analysis.

Simple Sounds.—If a steel bar or the prong of a tuning fork is made to vibrate through a short course at a uniform rate, part of its energy is transmitted to the surrounding air, which is compressed on a given side by the beat in that direction and rarefied

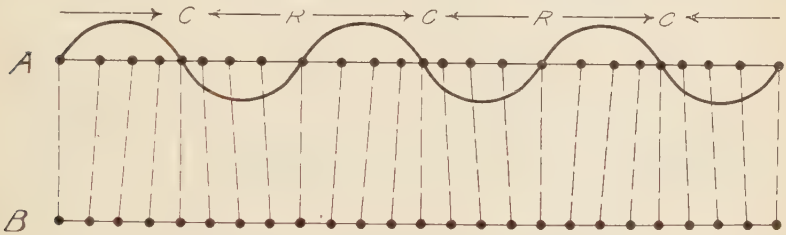


FIG. 67.—Diagram of sound wave. *A*, positions of particles of air; arrows indicate direction of displacement; *C*, condensation; *R*, rarefaction; *B*, particles of air at rest for comparison.

by the reverse movement. These alternate compressions and rarefactions are conducted outward from the source at a rate which at ordinary temperatures lies between 340 and 350 meters per second (about 1120 and 1150 feet). The vibrating source (supposing its movements to produce a single rate only) may vary in the amplitude of its movements, which will cause different degrees of vigor or intensity in the compressions and rarefactions produced, or in its rate, which will give rise to a greater or less number of waves per second. It is customary to diagram these air waves, as in Fig. 67, in which the base line represents the undisturbed condition of the air molecules, distances above this, displacement to the right and below this, displacement to the left, as indicated by the positions of the points on line *A*, which are to be compared with those at rest and therefore evenly spaced as on line *B*. The sine curve representing in this fashion the direction and degree of displacement has two points deserving special mention. The points of crossing with the base line represent *nodes*, or places of no displacement; the node on the descending portion (passing from left to right) is the center of a condensation, and that on the ascending portion the center of a rarefaction. The *phase* is that portion of the complete

wave occurring at that particular instant; in the diagram it will be determined by the distance along the axis measured from a specified point as, for example, the node on the ascending portion. Two series of waves are said to be "in phase," when the same phases of each wave are occurring simultaneously. Thus diagrammed, three waves of equal frequency but of differing amplitude would appear as in *A*, Fig. 68; three waves of differing frequency but of equal amplitude, as in *B*.

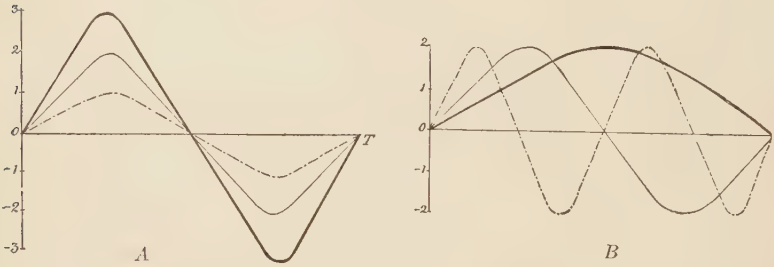


FIG. 68.—Method of diagraming amplitude and frequency. *A*, three waves of same frequency but varying amplitudes; *B*, three waves of equal amplitude but varying frequency. (Auerbach.) (Howell's Physiology, W. B. Saunders Co., Publishers.)

Physically many rates may be produced, but we are here concerned only with the limited range affecting the human ear, approximately 20 to 20,000 vibrations (cycles) per second.

Complex Sounds.—Although simple tones differ only in frequency and amplitude, it may easily be shown that these two features do not completely describe the sounds produced by musical instruments or the human voice. Our sensations vary in loudness with variations in the amplitude of the wave and in pitch with variations in the frequency. By hearing we can state the relative pitch of two notes produced by two musical instruments and adjust with great accuracy the two notes to the same pitch, as in tuning. When this has been done, however, and the two instruments are played with the same force so as to produce the same loudness, the two sounds are by no means identical, and with our eyes closed we can identify one as coming from a piano and the other as coming from a violin or call by name two persons singing the same note. What physical difference still exists between the sounds from the two tuned instruments that the ear may use as a basis of distinction?

We have said that the production of simple sounds is difficult. If a piano string sounding a certain note be touched lightly in the center so as to interfere with its vibration the sound will not cease but will continue with diminished loudness at a higher pitch—it will "jump an octave." This shows that in the vibrating string there was present another and higher frequency than the *funda-*

mental, or lowest rate from which we name the pitch. Careful physical analysis in such a case will show not merely one but a long series of differing rates of vibration or overtones. Such an analysis of the tone of a piano string is presented in Fig. 69, showing seventeen overtones in addition to the fundamental, or, according to another terminology, eighteen partials, of which the fundamental is the first. If now the violin is analyzed it will be found that a fundamental of the same frequency is present and many of the same

FIG. 69.—Timbre; the analysis of the complex sounds of a piano, violin and clarinet. The lines represent the fundamental and the detectable overtones; the height indicates the relative amplitude. (Fletcher.)

overtones, but that their number and relative intensity differ in a characteristic fashion. It is clear that here, as in most cases, we are dealing with a complex sound. Strings when plucked or bowed, as in most instruments, near one end, fall naturally into a variety of vibrations, swinging as a whole (the fundamental) as halves (first overtone), thirds, fourths and so on until the amplitude of vibration is too slight to be detected. A vibrating string, however, transmits but little of its energy to the air. All stringed instruments provide broad wooden or other surfaces which, taking up vibrations from the string, transmit them to the air in far greater degree than is possible with the string alone. Such "sounding boards" will of necessity have their own characteristic frequencies and these they will more strongly reinforce, giving the instrument its individual

tone which we recognize as its "timbre." A similar result is obtained from enclosed air spaces, such as the mouth, nasal cavity and sinuses in man.

How does the air beaten by such a variety of simultaneous vibrations behave? It is clear that at a given time and place but one process may be going on; the molecules may be suffering displacement in but one direction and at one rate. A complex wave form differing from the sine curves of Fig. 67 must result. A simple

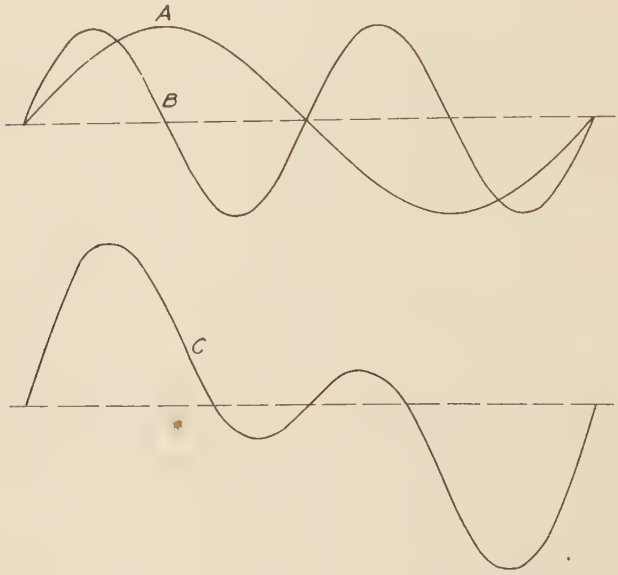


FIG. 70.—Complex wave. *A*, fundamental; *B*, octave of same amplitude; *C*, complex wave formed by algebraic sum of *A* and *B*.

case may illustrate this. In Fig. 70 two waves are diagrammed; A, the fundamental and B, its octave or first overtone, both of the same amplitude. In C is given the resultant complex wave. It may easily be seen that the complex wave at any point is the algebraic sum of the two component curves. Obviously the complex tones represented in Fig. 69 would be more intricate in form, but in every case a compound wave would result. Such compound waves are picked up by a telephone transmitter and carried electrically through space to a second diaphragm which reëxecutes the compound movement, or are recorded by the phonograph for preservation through time.

It is such compound waves of almost inconceivable complexity that reach the ears of animals and man, and from these the ear must sort in some fashion the various elements as when we recognize the voice of a friend in the confused roar of a city street.

THE RECEPTOR FOR HEARING.

What is the structure that performs this difficult physical feat? Grouping the structures on a physiological basis and omitting the non-acoustic labyrinth, which as we have seen has a different function from the auditory portion of the ear, we have: (1) The *essential receptors*, the hair cells in contact with which the fibers of the auditory nerve terminate; (2) grouped about these is a series of *accessory structures*, which may be divided into: (*a*) A sound-receiving apparatus, consisting of the pinna and the external meatus; (*b*) a sound-conducting and converting apparatus, consisting of the tympanic membrane, the ossicles and attached structures; (*c*) a sound analyzer located in the cochlea. The first two classes of accessory structures are wholly absent in fish and the analyzing mechanism, if present, must be extremely simple, as the cochlea is represented only by the far less complex lagena; these accessory mechanisms appear only in air-living vertebrates with the necessity for reception of air waves. Because of the greater weight of the medium as compared to air, water waves can more easily set solid bodies in vibration, and in the hearing of fish such vibrations are transmitted directly through the tissues of the head to the inner ear without any special mechanism. The utilization of the minute amount of energy carried by the air waves represents a far more difficult physical problem. How well it is solved is evinced by the fact that waves having an amplitude of less than $\frac{1}{2}$ micron (0.49×10^{-7} cm.) and an energy of 2.5×10^{-12} ergs may still be perceived.

Sound-receiving Apparatus. -The pinna in some animals serves to collect and concentrate the sound. A receptive reflex of turning the ear toward a source of sound occurs in such cases and is probably of service in locating the direction by the resulting changes of intensity; this may readily be seen in the horse. In man, however, this effect is negligible and the loss of the external ear has little effect on hearing. The external meatus serves to conduct the sound to the tympanic membrane and possibly has a slight reinforcing effect on some frequencies because of its resonance. The chief effect is protective; the delicate ear drum is shielded from mechanical injury and rapid changes of temperature. In amphibia, as, for example, the frog, where the external ear and meatus both are absent, the tympanic membrane, which is exposed to the same conditions as the other regions of the skin, and therefore requires the same protective strength, lacks the delicate mobility found in the mammal.

Sound-conducting and Converting Apparatus.—Air waves entering the external auditory meatus are conducted mechanically across the middle ear and delivered to the fluid in the inner ear. The

extremely delicate and important mechanism accomplishing this requires careful consideration. Essentially the middle ear consists of a cavity, across which is stretched, from the tympanic membrane to the fenestra vestibuli (fenestra ovalis), a chain of three small bones or ossicles with their attached ligaments and muscles. The cavity is derived from the first visceral cleft or gill slit and still communicates with the pharynx by the tuba auditiva (Eustachian tube).

The cavity is separated from the exterior by the tympanic membrane, the structure of which is important for an understanding of its function. Although thin (0.1 mm.), it consists of three distinct layers. On the exterior it is covered by the skin lining the external

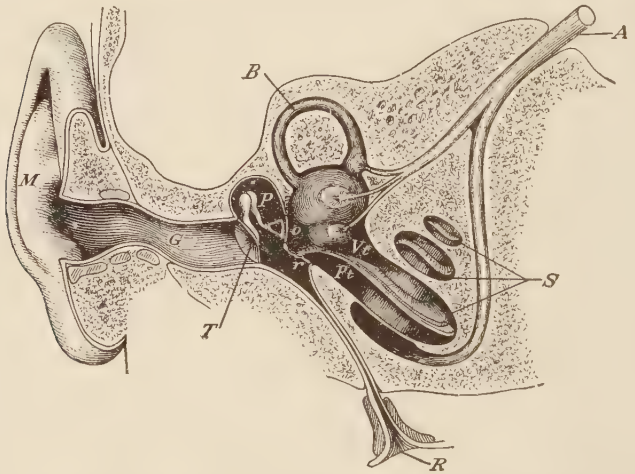


FIG. 71. —Diagrammatic section through ear. (Czermak.) *M*, *auricula; G*, external auditory meatus; *T*, tympanic membrane; *P*, middle ear with chain of ossicles; *o*, *fenestra vestibulæ* in which rests the foot plate of the stapes; *r*, *fenestra cochleæ; R*, pharyngeal opening of *tuba auditiva; B*, a semicircular canal; *S*, the cochlea; *Vt*, scala vestibulæ; *Pt*, scala tympani; *A*, acoustic nerve. (Martin's "Human Body," Henry Holt & Co., Publishers.)

meatus and on the interior by the mucous membrane lining the middle ear, which is continuous with that of the pharynx through the tuba auditiva. Between these two layers lie the connective-tissue fibers which give to the membrane its strength and characteristic shape. Before their disposition can be pointed out another feature must be noted. The handle or manubrium of the malleus, the first of the ossicles, is incorporated in a very intimate way in the tympanic membrane. It is covered by the mucous layer, and to it are attached the connective-tissue fibers. Those on the exterior side are radial in arrangement, passing from the distal portion of the handle of the malleus which lies near the center of the tympanic

membrane to the wall of the external meatus. Inside these are circular fibers somewhat less numerous.

The handle of the malleus is normally drawn inward by the pull of the tensor tympani muscle, so that the tympanic membrane forms a shallow funnel. Due to the elasticity of the circular fibers, the radial fibers are not straight but pass to their attachment in a slight outwardly convex curve, and in consequence the shape of the membrane is that of an umbrella turned inside out. If a spider web which contains both circular and radial fibers is touched in the center with the finger and drawn to one side the same shape is obtained, and for the same reason.

The position of rest of the tympanic membrane represents an equilibrium between the tonic tension of the tensor tympani muscle and the tension of the stretched elastic circular and radial fibers. As a result, its behavior is quite different from that of an ordinary stretched membrane, such as a drum head. In the first place, its displacement is accomplished with far less force, a very favorable feature when the small amount of energy carried by the air waves is considered. Secondly, the opposed tensions and the weight of the malleus and other ear bones effectually damp vibrations, thus preventing resonance and after-vibration and ensuring a faithful transmission of frequencies and no prolongation of a sound after its cessation. The tension of the tympanic membrane depends upon the degree of contraction of the tensor tympani muscle. Reflex contractions occur to tones of high frequency, and the muscle has been supposed by some to act as an accommodative mechanism adjusting the ear to different frequencies, but the experience of the few people having voluntary control over the muscle does not support this view.

Ossicles.—The malleus, as already stated, is attached by its handle to the tympanic membrane and from the handle passes the tendon of the tensor tympani muscle. The chief mass of the bone lies above the membrane and is attached to the walls of the tympanic cavity by three small ligaments which allow rotation of the head when the handle is forced inward. The incus, next in the chain, articulates with the malleus and is supported by one ligament. In its movement it rotates about a common axis with the malleus. The stapes or stirrup, the third bone of the chain, is articulated by its head with the long process of the incus, and its base is fixed to the walls of the fenestra vestibuli by elastic fibers. Its movements, therefore, like those of a piston, transmit pressure to the perilymph of the inner ear. Attached to it is the stapedius muscle, the contractions of which serve to tilt the base in the fenestra vestibuli.

When the tympanic membrane moves under impinging air waves the malleus and incus, acting as a bent lever, communicate the

motion through the stapes to the perilymph of the inner ear. This bent lever reduces the amplitude of the movement in the proportion of 3 to 2, correspondingly increasing the pressure; if, as claimed by some, the stapes tilts in the fenestra vestibuli, the leverage is still further increased. Another advantage is obtained because the area of the tympanic membrane is twenty times that of the base of the stapes. Taking into account the leverage of the ossicles, the total effect is to increase the pressure by more than thirty-fold. Movements of all parts of the chain of ossicles have been demonstrated; these are minute, the most extensive, that of the handle of the malleus, is but 0.75 mm.

It is possible to hear certain sounds in the absence of the tympanic membrane. These are usually of high frequency and, of course, at least fair intensity and are apparently conducted through the bones of the skull. Such "bone conduction" can readily be noted by holding a watch or the stem of a tuning fork against the head, or in a more striking manner if against the teeth. The portion of air-borne sound reaching the inner ear by bone conduction under normal conditions is negligible, although, as stated above, this is the normal route in fish exposed to the more forcible vibrations of water.

It is obvious that free movement of the tympanic membrane would be hindered by differences of pressure on its two sides. If the middle ear were a closed space such differences would often occur; the daily fluctuations in barometric pressure, or those due to ascent of mountains or descent into mines, are obvious causes, but even were the external pressure constant the internal pressure would be lowered through the absorption of soluble gases by the vascular walls of the middle ear. Equality of pressure is secured by the fact that, though usually closed at its pharyngeal end, the tuba auditiva is opened at certain times, chiefly during the act of swallowing.

REFLEXES.

Before taking up the complex and controversial questions of inner ear function it will be advisable to present the capacities of this part, the reflexes and sensations that it initiates.

The reflexes are all somatic and fall into two classes—characteristic simple receptive reflexes and complex anticipatory reactions similar to those of other distance receptors. Among the receptive reflexes the contraction of the tensor tympani to high tones has already been noted. In most animals there is a "pricking up" of the pinnæ and a turning of the eyes or of the head to sounds. These serve to put not only the ears but also the eyes in favorable positions for the reception of further stimuli. In man sudden loud sounds also cause winking; this is not properly a receptive reflex, but a simple protective reaction.

The second group of reactions include locomotion -pursuit and flight -which, as the case of smell and vision, may be anticipatory to a variety of consummatory reflexes.

SENSATIONS.

In richness of sensations the ear occupies a preëminence shared only by the eye, a fact that renders satisfactory presentation difficult. The attributes of auditory sensations arising from *simple tones* are usually considered to be: (1) *Intensity,* (2) *pitch,* (3) *volume* and (4) *duration;* for *complex tones,* or tones compounded of more than one frequency, there must be added the characteristic of (5) *timbre,* and for percepts arising from all tones (6) *position in time* and (7) *localization (position in space).*

Relations of Intensity and Pitch. Before considering intensity and pitch their peculiar interrelations must be pointed out. Intensity is looked upon as dependent upon the physical intensity of the stimulus, but whether this should be interpreted as energy per unit time or amplitude of vibration is not clear, and is further influenced by views of cochlear function. The total energy of a tone is proportional to the square of the product of the frequency and the amplitude, $E = (FA)^2$. Since this relation holds, the relative numerical values of thresholds or other data relating to intensity will be markedly different if expressed in energy or in amplitude. We will arbitrarily assume in the absence of conclusive proof of the correctness of either view that the intensity of the sensation is the physiological correlate of the amplitude of the vibration. Pitch is dependent upon the frequency of the stimulus. With a fixed frequency, variations of amplitude give changes in intensity of the sensation. With fixed amplitude, changes in frequency give changes in pitch and also in intensity. Recent investigations incident to the development of the telephone have made available unusually complete data on this relationship.

The determinations were made with a telephone diaphragm that could be electrically driven at various known rates and with various known amplitudes. Tested thus, a threshold is found for each frequency, but these are by no means equal. The least amplitude is required for frequencies between C_4 (2048) and C_5 (4096), and from this point of maximum sensitivity the necessary amplitude rises more and more rapidly as we pass to lower or to higher rates, as shown by the line marked threshold in Fig. 72. This represents a pressure variation of but 0.001 dyne, a sensitivity equalled only by the eye.

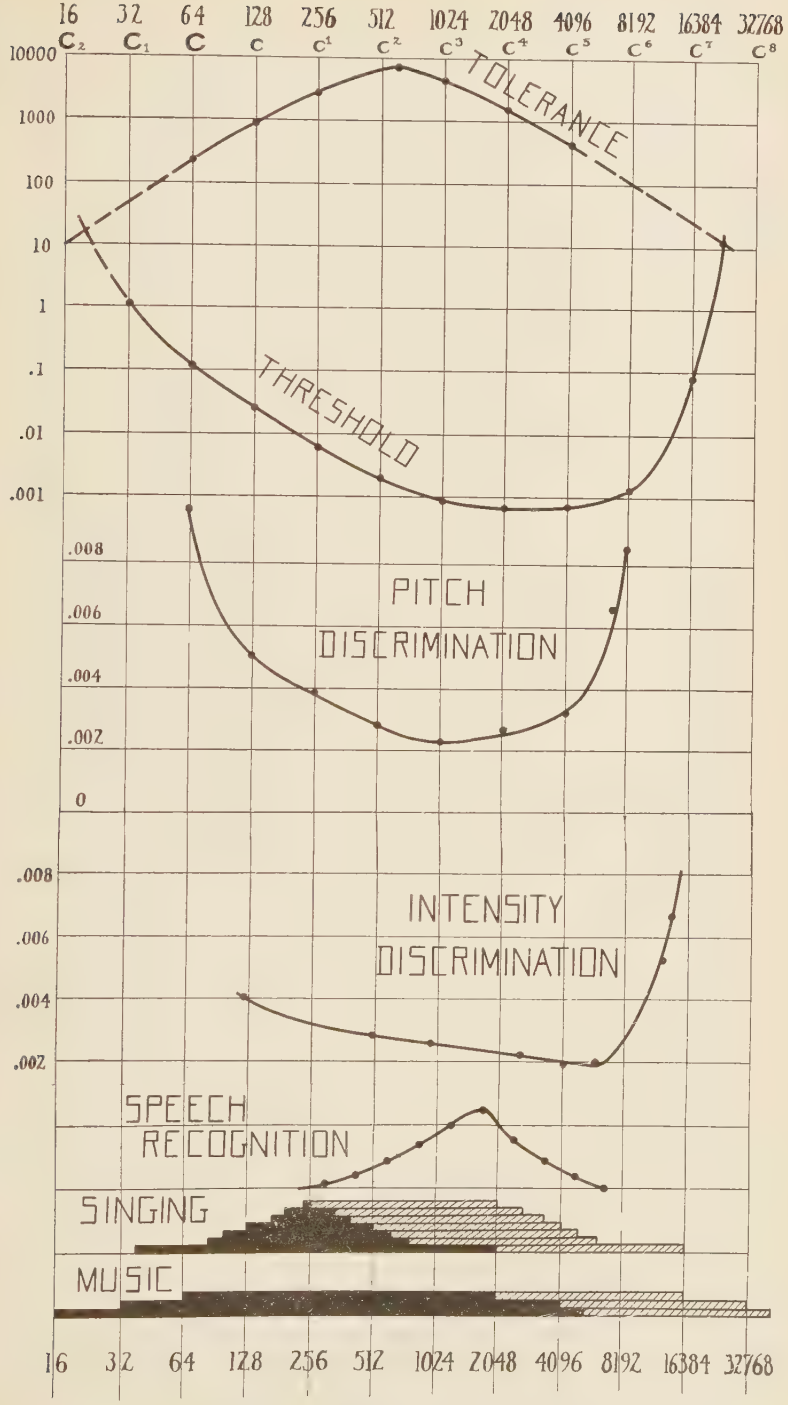
If the amplitude for each frequency is increased the intensity of the sensation increases and finally ceases to be purely auditory, including, according to Fletcher, tactile sensations from the tympanic membrane. Beyond this it becomes very unpleasant, indi-

cating that the functional range of the ear is being overstepped. This upper limit of tolerance, as it may be called, is not the same for all frequencies but, like the threshold, varies widely. It is notable that the greatest tolerance, as well as the greatest sensitivity, occurs at medium frequencies; actually the maximum amplitude tolerated lies between 512 and 1024, or slightly lower than the maximum sensitivity, which falls between 2048 and 4096. From this maximum the tolerance declines for either higher or lower frequencies. It will be noticed from the figure that as a result of this fact and of the variation in the value of the threshold, the functional range of the ear decreases rapidly in either direction from the central frequencies until extinguished by the intersection of the threshold and tolerance curves at about 20 and 20,000 vibrations. Above or below these points no purely auditory sensations are possible, since before the auditory threshold is reached tactile stimulation occurs.

The relation of these results to the "upper and lower limits of pitch," as they are usually called, should be pointed out. Such limits must be determined with reference to the amplitude of the sound waves; it is quite clear from the figure that for any particular level of intensity the limits of pitch would come at different points and the range would be less the less vigorous the stimulus. Since in the instruments commonly used for determining the pitch limits—Appunn's lamella or large forks for low pitches, Galton's whistle for high—the amplitude cannot be regulated or even measured, the results are of little significance. Other difficulties are also encountered. Overtones are present in almost all instruments; when testing the lower limit care must be used that it is not an overtone that is heard while the fundamental, an octave or more below, is recorded as the limit. The pitch of the Galton's whistle is so influenced by the air pressure used that when blown with a bulb it is unreliable; the commonly recorded upper limit of 40,000 is due to errors in the use of the whistle.

We may, therefore, think of the functional range of hearing as bounded for each pitch by intensity limits which converge at both high and low frequencies and for each intensity level by pitch limits which converge at both small and large amplitudes. With these relations of intensity and pitch in mind, we may turn to a survey of all the attributes.

FIG. 72.—The ear and speech. These are represented on a common frequency scale of octaves: (1) the threshold and upper limit of tolerance for the ear (Fletcher) with a common scale of amplitudes; (2) pitch discrimination expressed as a ratio; (3) intensity discrimination; (4) relative importance of the different frequencies in the recognition of speech (Fletcher); (5) range of singing voice, the bottom bar represents the extreme range with three octaves added for overtones, the height of the solid black area shows the number of registers in which a particular note occurs, the hatched portion, 3 octaves of overtones; (6) range of music, the lower black bar the extreme notes used, the second bar the range of the piano, the top bar the more used range, the hatched portion 3 octaves for overtones.


16 32 64 128 256 512 1024 2048 4096 8192 16384 32768
C2 C1 C c c1 c2 c3 c4 c5 c6 c7 c8
10000
1000
100
10
1
.1
.01
.001
TOLERANCE
THRESHOLD
.008
.006
.004
.002
0
PITCH
DISCRIMINATION
.008
.006
.004
.002
INTENSITY
DISCRIMINATION
SPEECH
RECOGNITION
SINGING
MUSIC
16 32 64 128 256 512 1024 2048 4096 8192 16384 32768

Intensity.—We have seen that, although intensity varies with the amplitude of the sound waves, it is also affected by pitch. A particular amplitude level does not give at different frequencies the same intensity of sensation, but paralleling the threshold is loudest for those frequencies having the lowest threshold. If we pass from this region of maximum loudness to frequencies above or below, without changing the amplitude, the sound becomes less intense until finally the threshold is reached and it is no longer heard. Since the region most used in music lies below the frequencies giving maximum loudness it follows that of two notes of equal amplitude the higher has the greater intensity. This statement would also be true of energies if these are substituted for amplitudes.

The power of discriminating intensity (difference threshold) varies both with amplitude and frequency. With moderate amplitudes a change of 10 to 20 per cent in amplitude is appreciated, but as the threshold for any given frequency is neared the perceptible change rises rapidly to 30 or 40 per cent. It is possible that a similar increase occurs as the limit of tolerance is approached, but the data are incomplete on this point. The variation of intensity discrimination with frequency parallels the threshold, being lowest at 2000 to 4000 and rising with either lower or higher frequencies (Fig. 72).

Pitch.—Pitch is, as we have seen, the correlate of frequency. The upper limit is markedly influenced by age; children can hear higher frequencies than can adults; the range is reduced by about 1000 vibrations for each ten years between the ages of fifteen and seventy-five years. This is possibly due to a decrease in the responsiveness of the sound-conducting apparatus of the middle ear, a process recalling the decrease with age in the range of accommodation of the eye (page 612).

The discrimination of pitch is a matter of more than common interest because of its relation to music. It varies with, but is no simple function of, frequency. At both high and low frequencies the power of discrimination becomes distinctly less; in this it follows the intensity threshold.

The picture will vary, depending upon what scale is used to measure pitch discrimination. Certain writers have expressed this in the actual number of vibrations by which two discriminable pitches differ. Thus represented, pitch discrimination becomes rapidly less keen at high frequencies and for some observers also at low frequencies.

The other method is to represent the difference as a ratio to the frequency tested. All musical scales and their subdivisions are based on ratios, but, although pitch discrimination sets frequency limits above and below which music cannot go, the scale is not based upon pitch discrimination alone, but also on the capacity

for fusion (page 560), shown by notes in the octave or other simple relations. Expressed as a ratio, pitch discrimination is at its best in the region of c_2 to c_4 (Fig. 72), from which it becomes rapidly less keen as we pass to higher or lower pitches. Pitch discrimination is thus seen to recall the threshold for intensity and to correspond in a remarkable degree with the critical frequency region of speech and music.

Volume.—Volume is a less commonly recognized attribute of auditory sensations than are intensity and pitch. Strangely enough, it apparently depends upon the same two physical variables—amplitude and frequency; it has been found to vary with both, although some claim that its primary dependence is upon amplitude. At equal amplitudes low tones are felt to be large and massive and high tones small and concentrated; at equal frequencies the more intense or louder tones are the larger. That these are, however, more than variations of pitch or intensity is indicated by two facts. In the first place the discrimination for volume is less keen than for either pitch or intensity; for example, a change of frequency may be sufficient to cause a change of pitch without causing a change of volume. In the second place, the relation of the threshold for volume to the changes in frequency or in amplitude is different in each case from that of the threshold for pitch or for intensity.

Duration.—In general, the attribute of duration in auditory sensations is similar to that in other cases and requires no special comment beyond noting that it plays an important part in music.

Certain time relations of the stimulus to the sensation are, however, of interest. A sensation of recognizable pitch may arise from a very few vibrations, variously stated as from 2 to 5, and an interruption of a continuous tone cannot exceed 0.03 second without interrupting the continuity of the sensation. Both facts speak for the rapid action and highly damped character of the sound-transmitting apparatus of the middle ear.

Even shorter time differences are found to have physiological consequences in binaural hearing. Thus if the same sound is led separately to the two ears a difference in its time of incidence of 0.00004 second or more causes a difference in localization; this will be further discussed under binaural hearing.

Complex Tones.—The great majority of tones with which the ear deals are complex tones compounded of many frequencies with their various intensities. We have already pointed out that the form of the complex wave, for example, from different musical instruments, differs, or, to express it in terms of the analysis of the wave, the sound differs in the number and relative amplitudes of the component frequencies or partials. It is by this difference called *timbre* that we distinguish the tones of two instruments tuned to the same pitch; although both have the same fundamental

rate, the number and relative vigor of the overtones still differ and are readily recognized. The same is true of the voices of different persons.

Attention will enable even the unmusical to recognize in a complex tone some of the differing frequencies; the trained ear of a musician can analyze with great exactness the complex tone into the majority of its constituent elements. Any theory of function of the inner ear must explain this power of analysis in which the ear surpasses any other of the receptors.

Fusion.—Although such analysis is possible, it is by no means the only or the chief tendency in auditory sensations. Three other distinct tendencies are recognizable in complex tones. The component tones may fuse or combine in an intimate way—they may react on each other to develop new tones not present in the original, or to reduce or eliminate elements originally present.

Fusion is a blending of two tones into one uniform impression of sound in which the elements can be distinguished, but in which the unity is more conspicuous. Fusion occurs between pitches standing in certain relations, but is entirely absent from slightly different relations. The most perfect fusion occurs when the relation is that of the octave, that is, when one frequency is double that of the other. It is notable that the octave relation occurs more often than any other in the normal series of overtones, and that for this reason the overtones of two notes representing an octave interval have in common a greater number of frequencies than another combination. In the subjoined table are given the first ten partials of a tone with the frequency of x vibrations and the corresponding partials of the octave of $2x$ vibrations:

$1x$	$2x$	$3x$	$4x$	$5x$	$6x$	$7x$	$8x$	$9x$	$10x$
	$2x$	..	$4x$	..	$6x$	..	$8x$	..	$10x$

It will be seen that in the first series the octave occurs five times—$1x$ to $2x$, $2x$ to $4x$, $4x$ to $8x$, $3x$ to $6x$, $5x$ to $10x$; often the partials number more than ten, and this relation would be correspondingly more numerous. In the two series five identical frequencies occur—$2x$, $4x$, $6x$, $8x$, $10x$. The octave is thus the interval which is most often experienced, and it presents more elements in common than any other pair of tones. Both these factors have been considered as influencing fusion; the development of this and other relations important in music lie outside the scope of the present work.

Other intervals fusing readily are 2 to 3, 3 to 4, 4 to 5, 5 to 6 and 3 to 5 (2 to 4, 6 to 8, 6 to 10, 8 to 10 and the like may obviously be reduced to the octave or one of the above ratios). On the other hand, ratios such as 8 to 9 and 15 to 16 fuse with difficulty or not at all. In general, although musical customs and taste vary from country to country and from age to age, simple numerical relations

fuse and are considered harmonious and pleasing when sounded together or sound similar when they follow one another, whereas the more complex relations are unpleasing or discordant.

Beats.—The new elements developed in a complex tone are *beats* and *combination tones*. If two slightly differing frequencies reach the ear simultaneously there is a characteristic shrinking and swelling of the intensity (and possibly volume); these variations are known as *beats*. If, for example, two forks, one with a frequency of 256 and the other of 258, are sounded together the complex wave continually changes in character. When the two frequencies are in phase the combined effect is intensified, since condensation is added to condensation and rarefaction to rarefaction. This condition is altered by the gradual gain of the higher frequency upon the lower until this amounts to one-half a phase, when the intensity will be greatly reduced by the combination of a condensation with a rarefaction. This will occur at one-quarter second after coincidence. At one-half second the phases will again coincide, giving increased amplitude. Two beats will, therefore, occur per second. The number of beats is in general equal to the difference in frequency between the beating tones. Beats may be distinguished up to about 30 per second, after which they fuse.

Combination Tones.—Related in an obscure manner to the phenomenon of beats are the tones that may be recognized when two simple frequencies differing fairly widely are sounded simultaneously. For example, in the complex sound resulting from rates of 200 and 300, a *difference tone* of 100 and a *summation tone* of 500 may be detected. These *combination tones* are probably more important than ordinarily supposed. The tone of any musical instrument contains a fundamental and a series of overtones, sometimes ten or more in number, each of which exceeds in frequency the preceding by an amount equal to the fundamental, thus furnishing a long series of difference tones reinforcing the fundamental. A striking instance of their effect is afforded by a complex tone from which the fundamental and the first one or two overtones have been removed. This is not possible mechanically, but can be accomplished electrically by transmitting the tone by telephone and placing in the circuit a "filter" which will remove the desired frequencies. The resulting tone does not differ in pitch from the original, the fundamental apparently being replaced by the difference tones. If an increasing number of overtones are removed the first change noted is in the timbre and not in the pitch.

The explanation of combination tones offers many difficulties. Unlike beats, they have no simple physical counterpart. They do not appear in the results of analysis of the complex wave by graphic or mathematical means; all that are obtained are the original components. If an analysis by resonators occurs in the ear the combi-

nation tones still remain to be accounted for. Some workers have claimed that the combination tones had a physical existence in the air or were generated in the tympanic membrane or some other part of the conducting apparatus of the ear. Resonators and other devices, however, fail to detect them in the air and they may be heard by ears in which the tympanic membrane is lacking. They may result from the working of the cochlea, but in the absence of more data this is mere speculation.

"Masking."—Simultaneous tones may also have another effect—one may interfere with, or *mask* the other. Recent data show that the threshold of tones of higher frequency than the masking tone is increased; lower tones are somewhat affected near the masking frequency but those still lower are unaffected. Intensity was the basis of these determinations. It is possible that some phase of fusion is involved in which the analysis is favored by more intense tones. This view is not, however, supported by the fact that when the tones are led to separate ears the masking effect is very greatly reduced. It would be desirable to repeat this work with volume as one of the criteria. Apparently the factors involved in "masking" tend to alter the timbre of a complex sound when its amplitude is considerably changed.

Position in Time.—The percept of position in time requires no special consideration, since it presents no features markedly different from those encountered in other receptors. It is notable, however, that the time relations of tones play a conspicuous part in music.

LOCALIZATION.

The power of localizing or placing in space the source of an auditory sensation is well marked in man. In this regard hearing is intermediate between smell in which localization is negligible and vision in which localization reaches its highest development.

As in the eye, localization is chiefly dependent upon the combined action of two symmetrically placed receptors, that is, localization is *binaural*. *Monaural* localization is very limited and uncertain. In man there is some change of intensity with head movements, the maximum intensity occurring when the source of sound is opposite the meatus. When not in this position some clue is given by the timbre of the sound which is apparently affected by diffraction in passing about the head, selective reflection from the pinna or similar factors. For this reason complex sounds are better localized than are simple ones.

Binaural localization is far more exact and rapid in mammals and apparently in birds. In mammals with large movable pinnæ these are apparently an important factor. Most of our data are, however, from man in whom the pinnæ have little significance, and

it is this form of localization that we will discuss. *Differences in the sensation arising in the two ears from a single sound source are the basis of our judgment of position.* Localization is chiefly a matter of horizontal direction. Vertical direction and distance are based on less definite and reliable clues and are often grossly in error. Thus a slight shift of the sound source from the median plane is readily detected, whereas positions in the median plane in front and behind the head are often confused. Three differences in stimulation have been found to influence localization, differences of *intensity,* of *time* and of *phase.*

Intensity Differences.—A sound reaching the two ears from a source not in the median plane tends to reach the nearer ear in greater intensity and is correctly judged to lie nearer that ear. Where there is a slight difference of sensitivity in the two ears this is apparently compensated for by experience, since a sound source equally distant is so judged, although the two sensations differ in intensity. If great inequality of acuity is present localization is unreliable or impossible.

Time Differences.—That time is a factor in localization has been more recently discovered. If two discrete sounds of equal intensity are led to the two ears, and the time of this incidence carefully regulated, the following results are obtained. When the difference in time does not exceed about 0.00003 second they are perceived as one sound and localized in the median plane. With increased difference in time the resulting sound is still considered as single, but localized toward the ear first stimulated. When the difference in time exceeds 0.002 second two sounds are heard, and the observer can tell whether the right or the left ear is first stimulated.

Phase Differences.—The third factor of phase difference has also been carefully investigated. Ordinarily the sound waves from a median source reach the two ears in phase, that is, the two condensations reach the two ears simultaneously. If the source is displaced laterally, the phase on the nearer side will lead by the small interval representing the difference in time of air conduction to the two ears. This situation has been experimentally checked by the separate conduction to the two ears of a sound of constant amplitude, in which the phase could be altered, as, for example, by conduction through tubes of adjustable length. If the phase reaching the right ear is made to lead by shortening the tube on that side, there is an apparent lateral shift of the source to the right. This increases up to a maximum displacement, when the lead is nearly one-half a wave length. Beyond this a further advance of the phase for the right ear places the phase for the left ear in the lead and the sound shifts to the left side. With further advance of the phase for the right the lead of the left becomes less and the sound shifts toward the median plane until, with a difference of an entire

wave length, the ears are again "in phase" and localization is again median.

As Boring has pointed out, the difference of phase is really one of time, and the two criteria are but different aspects of the same physical situation. It has also been found in testing with differences of time that the intensities must be equal; a slightly later stronger stimulus may balance an earlier weaker one. It is, therefore, probable that the contrasted cerebral processes are the same in all these cases; if equally intense, the sound is localized medially, and intensity may result either from the amplitude of the stimulus or the preponderating effect of an earlier initiated activity.

It is notable that the delicacy of localization may be increased by an effective increase in the interaural distance; this may be accomplished by leading the sound from paired horns several feet apart by separate tubes to the two ears. Such a device has been successfully used in locating airplanes at night.

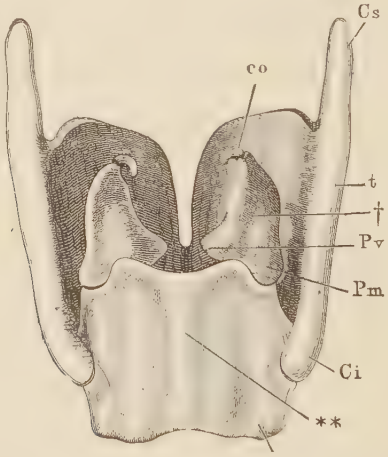


FIG. 73.—The important cartilages of the larynx from behind. *t*, thyroid; *Cs*, its superior, and *Ci*, its inferior, horn of the right side; **, cricoid cartilage; †, arytenoid cartilage; *Pv*, the corner to which the posterior end of a vocal cord is attached; *Pm*, corner on which the muscles which approximate or separate the vocal cords are inserted; *co*, cartilate of Santorini. (Martin's "Human Body," Henry Holt & Co., Publishers.)

VOICE.

The production of sounds is fairly widespread among animals, although notably more common among land than aquatic forms, but regulation and control of the sounds produced is practically confined to birds and mammals, and reaches distinctly its highest development in man. It is particularly important to consider the voice in the light of the capacities of the ear, as between the two we might well expect a definite relation.

Voice and Speech.—The production of voice in man and various other mammals takes place in the larynx where vibrations in the expiratory current of air are caused by the vocal cords. These sounds together with certain others are used in speech, a purely human faculty. We will consider first the larynx and the mechanism of voice production, second, the character of the sounds utilized in speech and last their relation to the features of hearing discussed above.

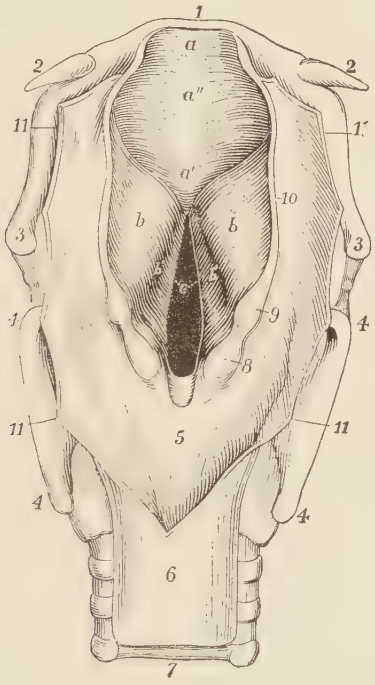


FIG. 74.—The larynx viewed from its pharyngeal opening. 1, 2, 3, the hyoid bone; 4, thyroid cartilage; 5, anterior wall of pharynx covering cricoid cartilage; 6, upper end of esophagus; 7, trachea; 8, 9, 10, the arytenoepiglottic folds; *a*, epiglottis; *c*, the glottis, the lines point to the free vibratory edges of the vocal cords; fold between *b* and *b'*, the false vocal cords. (Martin's "Human Body," Henry Holt & Co., Publishers.)

Larynx and Voice Production.—The *larynx*, a modified portion of the trachea at its junction with the pharynx, consists of a framework of cartilages united by joints and membranes and capable of being altered in position by small muscles. The more important cartilages are the *cricoid*, the *thyroid*, the paired *arytenoids* and the *epiglottis* (Fig. 73). The cricoid, at the base, consists of a ring widest behind. The thyroid, the largest of the cartilages, forms the prominence known as the "Adam's apple;" it has the shape of an incomplete

ring, wide in front and interrupted behind where it articulates with the cricoid. The two arytenoids are triangular in form and articulate by their bases with the cricoid near the mid-line posteriorly; their apexes are directed up and lie close together.

Arising from the lateral walls of the interior of the larynx are two pairs of folds, the upper or false, and the lower or true *vocal cords*. The latter, in contrast to the remainder of the larynx, are covered with flat non-ciliated cells so thin that through them may be seen the yellowish color of the ligaments which give support to these folds. The ligaments are stretched from the anterior median margin of the thyroid to the median upper angles of the movable arytenoid cartilages. By means of a group of small muscles over which we have unusually delicate control, the inner margins of the cords may be separated and relaxed as in quiet breathing, leaving an unobstructed passage for the air, or may be tensed and approximated, so that the air current sets them in vibration.

The frequency produced by the vibration of the vocal cords will depend upon their length, elasticity, tension and degree of separation and upon the pressure of air in the trachea. The length cannot be altered but, as is well known, changes with age, adults having longer cords and lower-pitched voices. During the period of rapid growth of puberty this lengthening is most marked in boys the voice "breaks;" in girls, although rapid, the change is less conspicuous. The factors of tension and separation are under voluntary control and are represented by a cortical center. The delicacy and rapidity of control in ordinary speech is remarkable, the fineness of adjustment in a trained and skilful singer representing, perhaps, the most exquisite of our muscular coördinations. The amplitude of the wave is dependent upon the pressure of the air and is controlled by the respiratory muscles.

The sounds so produced are modified by the resonance of the cavities communicating with the respiratory system, the pharynx, the mouth, the nasal cavities and the connecting sinuses. To the size and shape of these cavities is due the timbre of individual voices.

SPEECH.

The sounds used in speech consist of modification of the laryngeal sounds and certain additional sounds produced wholly by the passage of air through the mouth while the lips and tongue are held in certain positions, as in the case of the consonants *p*, *t* and *s*.

Frequency Range of the Voice.—The human voice has a range of about two octaves and certain rare voices may compass three and one-half octaves. The singing range is usually stated to be from F (87) for the lower bass to g^2 (768) for the upper soprano. The extremes on record are F_1 (42) and c^4 (2048). It must be remem-

bered, however, that these are the fundamental frequencies; overtones covering two or three octaves above these figures are also present.

The Distribution of Energy in Speech.—The average amplitude for the different frequencies found in spoken words has recently been determined and presents an interesting picture. The maximum value lies at a very low frequency, not far from 128, and while the measurable energy extends beyond 4000, half of the total energy is found below a frequency of about 400.

This picture is not paralleled, however, by the importance in speech recognition of the various parts of the voice range. This difference apparently rests on two facts: First, the threshold, or minimum effective amplitudes, as will be recalled, are far greater for the lower frequencies, so that the greater energy here present only serves to compensate to a certain extent for the higher thresholds. In the second place, the loudest frequencies are not necessarily the most critical. The question of the relative significance

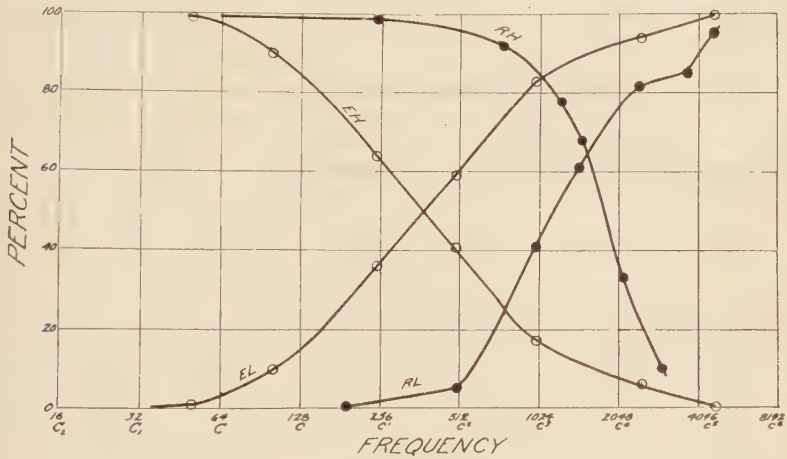


FIG. 75.—Distribution of energy in, and recognition of speech. *EL*, energy transmitted by frequencies below, and *EH*, by frequencies above the frequency indicated; *RL*, recognition of speech containing only that frequencies below, and *RH*, only those above the frequency indicated. (Data from Fletcher.)

of different elements in the recognition of speech, although important, is complex; its attempted analysis by telephone engineers, while probably subject to revision, is nevertheless very interesting. It is possible to remove certain frequencies from speech transmitted by telephone by the use of electric "filters" in the circuit. If low frequencies are removed the loss of recognition is very slight, being only 5 per cent for all frequencies up to 500, by which time 60 per cent of the energy has been eliminated. Beyond this the effect on

speech is rapid, and by the time 4000 vibrations is reached but 5 per cent can be recognized. By the removal of high frequencies similar results are obtained, both clearly indicating that the critical frequencies for speech lie between 500 and 4000. This method of determination, it will be noted, unlike the notation for the singing voice, includes the overtones.

If the intensity of ordinary speech is increased or decreased, a wide range has been found compatible with recognition. It is thus claimed that an increase in intensity of a hundredfold or a decrease of a hundred thousandfold is without marked effect on the ability of the recipient to recognize the words spoken. In the absence of more evidence as to whether the intensity of sensation depends upon amplitude or upon energy, however, these figures must be accepted with caution.

Hearing and Speech.—It is instructive to compare the threshold and limit of tolerance of hearing shown in Fig. 72 with the facts just presented for the voice and music. The critical range of speech which we have set at 500 to 4000 includes, it will be noticed, the maximum sensitivity of the ear (2000 to 4000) and extends far enough below to include also the maximum tolerance (500 to 600). Within this same range lie also the greatest power of pitch discrimination (if this is expressed as a ratio to the frequency, 1000 to 2000) and apparently the keenest intensity discrimination for the different pitches. This region is thus the most significant for hearing and speech from whatever angle it may be viewed.

The range of the singing voice, if we include the extreme records and add two or three octaves to account for the overtones (the spoken voice often shows ten partials or about three and one-half octaves), includes practically the entire frequency range of the ear. The range used in music is given as 40 to 4700; this with two octaves for overtones is approximately that of the singing voice. The upper limit of the frequencies suitable for music is apparently set by the rapid rise of the pitch threshold near 4000, which interferes with and soon vitiates the judgment of even trained musicians. An octave or so above this the intensity threshold also rises rapidly and soon frequencies of ordinary amplitude cannot be heard. Even the higher notes of the piano are thin and relatively unmusical probably because we fail to hear the upper partials.

Taken together, these facts show a remarkable parallelism between the sounds utilized by man in speech and music and the functional capacity of the ear.

Deafness.—Various defects may impair hearing and merit the term deafness if they interfere with the recognition of ordinary speech. The conducting apparatus of the midde ear undergoes with age, as we have seen, changes reducing its power of transmission, particularly for the highest tones. Pathological changes in the

articulations of the ossicles thus reducing their flexibility cause a form of deafness in which there is a greatly reduced sensitivity for low tones. Certain changes in the cochlea may also cause reduced sensitivity for various frequencies, often those in the higher part of the range. Deafness may this include reduced sensitivity, either in general or for some single region, or even a very limited range of frequencies. It is obvious that defects invading the critical zone for speech recognition will be the most troublesome.

FUNCTIONS OF THE COCHLEA.

We still have left to consider the functions of the cochlea. From the features of the sensations previously considered, it is obvious that a satisfactory theory of cochlear function will have to account for at least the following facts: Sensations of pitch between frequencies of approximately 20 and 20,000, including about 1500 steps at moderate intensities; sensations of intensity over a wide range of amplitudes, comprising perhaps 270 steps at ordinary frequencies, or to combine the two, sensations differing in pitch or intensity to an estimated number of over 300,000; the recognition within certain limits of two or more simultaneous frequencies; sensations of volume to an unknown number; the fusion and the "masking" of simultaneous tones; the occurrence of combination tones representing frequencies not present in complex tones. Further, such a theory must account for the facts of localization, certain pathological conditions, such as tone lacunæ and islands, and a small body of experimental results obtained by injuring the cochlea through exposure to particular sounds.

A review of the literature shows at least twenty reasonably distinct hypotheses, many of them recently proposed or at present actively supported, conclusive proof of our ignorance of cochlear function. In the present state of uncertainty, and in view of a renewed activity in experimental work, the data from which will undoubtedly modify existing views, it will be unprofitable to do more than sketch the outlines of a few representative hypotheses, introducing them by such few facts as seem generally agreed upon.

Anatomy of Cochlea and Organ of Corti.—To consider the function of the cochlea we must recall its anatomy. The cochlea comprises a portion of the membranous labyrinth lodged within the osseous labyrinth of the temporal bone. This portion, derived from the otic vesicle and containing the essential receptors, consists of an elongated canal, the *cochlear duct,* triangular in cross-section and containing endolymph. Lying parallel to and in contact with the cochlear duct are two canals filled with perilymph, the *scala vestibuli* and the *scala tympani.* The combined canals present an approximately circular cross-section. The canals are coiled in a

spiral roughly resembling a snail shell, whence the name cochlea. The scala vestibuli and the scala tympani communicate by the helicotrema at the apex of the cochlea beyond the blind end of the cochlear duct.

In the osseous labyrinth two openings communicate with the middle ear, the *fenestra vestibuli* and the *fenestra cochleæ*. In life the fenestra vestibuli which would lead into the scala vestibuli is closed by the base of the stapes and the elastic fibers binding it to the

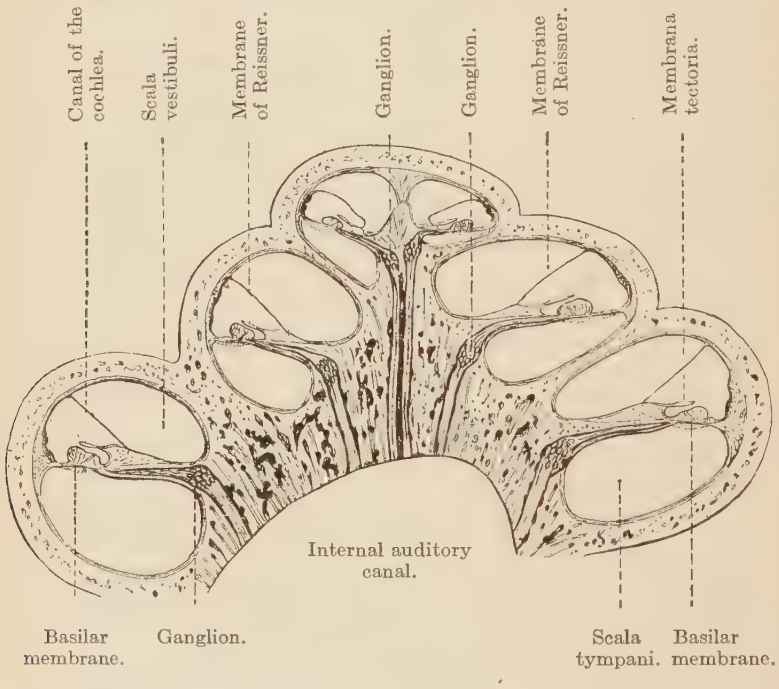


FIG. 76.—Section through axis of human cochlea (diagrammatic). (From Schäfer's "Essentials of Histology," by permission of the author.)

margins of the fenestra. The fenestra cochleæ is closed by the *secondary membrane* of the tympanum. The general relations of these parts are shown in Fig. 71.

The important *organ of Corti*, containing the essential receptors, the *hair cells*, lies within the cochlear duct. The cochlear duct is separated from the scale tympani by the *basilar membrane*, which consists of a great number of fibers stretched radially from wall to wall of the cochlea. Its length is stated by various anatomists at from 33.5 to 35 mm.; its width at the base, from 0.16 to 0.21 mm.; at the apex, from 0.36 to 0.52 mm. Upon it rests the organ of

Corti, the essential feature of which is a series of hair cells arranged in four or five longitudinal rows supported with the hairs directed away from the basilar membrane. Projecting over the organ of Corti, and probably in contact with or attached to the hairs, is the *tectorial membrane*, composed of fine fibrils imbedded in a glutinous matrix. The hair cells are supplied by nerve fibers of the bipolar nerve cells lying in the *spiral ganglion* of the axis or modiolus of the cochlea, the axones of which form the acoustic nerve.

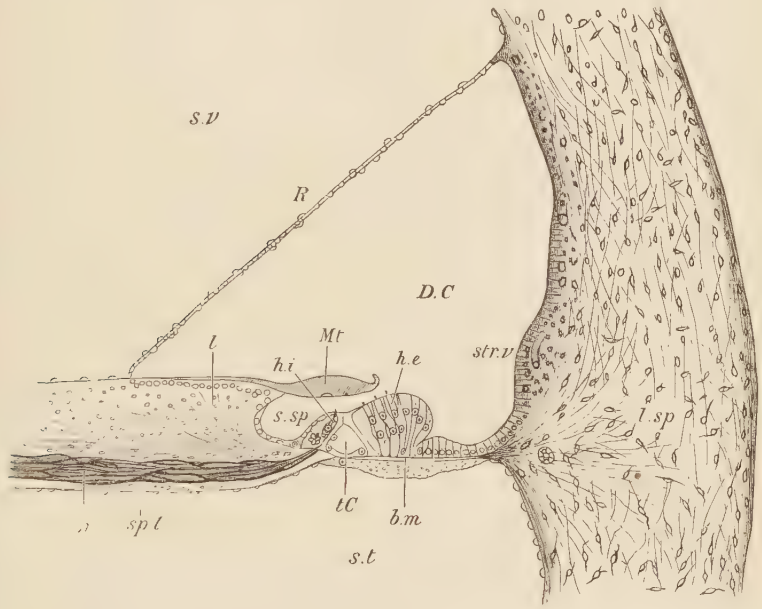


FIG. 77.—Axial section of the first turn of the human cochlea. (Retzius.) *s.v.* scala vestibuli; *s.t.*, scala tympani; *D.C.*, cochlear canal; *sp.l.*, spiral lamina; *n*, nerve fibers; *l.sp.*, spiral ligament; *str.v.*, stria vascularis; *s.sp.*, spiral sulcus; *R*, section of membrane of Reissner; *l*, limbus laminæ spiralis; *M.t.*, tectorial membrane; *tC*, tunnel of Corti; *b.m.*, basilar membrane; the tectorial membrane should be represented in contact with the hair cells: *h.i.*, *h.e.*, internal and external hair cells. (From Schäfer's "Essentials of Histology," by permission of the author.)

The vibrations of the external air are ultimately delivered to the perilymph of the inner ear through variations in the pressure of the base of the stapes on the perilymph at the fenestra vestibuli. The total mass of the ossicles, perilymph and endolymph is so small (0.05 + 0.12 = 0.17 mg.) and their dimensions so minute, in comparison with the wave length of sound in bone and water (which amounts to 3 and 1.5 m. respectively for a frequency of 1000), that mass movements only of the ossicles and lymph are thought possible.

Movements of the stapes are ultimately compensated for by cor-

responding excursions of the membrane closing the fenestra cochleæ. The pressure variations first affect the perilymph of the scala vestibuli. This communicates by the helicotrema, at the apex of the cochlea, with the scala tympani ending at the fenestra cochlea, while between the two scalæ lies the cochlear duct containing endolymph and separated by the membrane of Reissner from the scala vestibuli and by the basilar membrane from the scala tympani. Since both membranes are flexible, these are probably displaced by changes of pressure; actual movement of the lymph from one scala to the other through the helicotrema must be exceptional.

The relation of the fibers of the auditory portion of the eighth nerve to the hair cells is such as to make it obvious that these are the essential receptors. It is equally clear that the stimulation is mechanical. This might occur in several ways. Movements of the tectorial membrane might bring it in contact with the hairs of the hair cells or movements of the basilar membrane and, therefore, of the entire organ of Corti might bring the hairs against the tectorial membrane. It is more probable, however, that the hairs are normally in contact with or imbedded in the tectorial membrane in which case the movement of both membranes would cause a bending of the hairs. With this introduction before us we may take up a brief consideration of certain prominent hypotheses.

Helmholtz's Resonance Hypothesis.—Of the hypotheses of the workings of the inner ear, the most conspicuous is that of Helmholtz. Although many features have been criticized and some find few supporters, this hypothesis probably has more adherents than any other. This is undoubtedly because it was based on an intimate and thorough knowledge of all phases of hearing, whereas many of the other views have been suggestions regarding a single feature of audition, or modifications of previous views.

Its central feature is that the simultaneous recognition of different frequencies is best explained by the presence of a series of resonators. This series is to be found in the basilar membrane, which is of varying widths in its different parts, being widest at the apex and narrowest at the base of the cochlea. The fibers are transverse and, being relatively independent, may vibrate separately, or at least short segments of the membrane may so vibrate. A particular frequency would, therefore, cause movement of the appropriate resonators and stimulation of those hair cells resting on that part of the basilar membrane. *Pitch* would, therefore, depend upon the hair cells affected. Before the establishment of the all-or-nothing principle of nerve conduction, *intensity* was not considered as presenting any particular physiological problem and was not treated in any detail by Helmholtz. In its present form the hypothesis would apparently base intensity upon the number of fibers stimulated. A more intense tone would, therefore, involve

hair cells on either side of those giving the exact pitch, and it is necessary to postulate that the region of maximal stimulation would fix the pitch. This is considered by some a serious difficulty. *Volume* presents difficulties that have not been specifically met by adherents of this view. *Analysis* of complex tones by the resonance of the appropriate portions of the basilar membrane is readily explained; indeed, as suggested, this is the point of departure of the hypothesis. *Combination tones*, however, present grave difficulties. Analysis, as has been pointed out, does not give them, and if they are without physical existence in the air they must be explained by the mechanism of the cochlea. *Tone lacunæ*, or *islands*, found in some defective ears where gaps occur in an otherwise normal region of pitch perception, or certain pitches are perceived in an otherwise deaf range, may be readily accounted for by defects in the particular resonators or their attached hair cells. Certain experimental evidence has been cited as favoring this hypothesis. Animals have been exposed for long periods to certain frequencies, such as those of continuously sounding whistles and the cochlea subsequently examined for evidence of localized injury to the organ of Corti. Although in some cases the degeneration due to high-pitched tones was found near the base, as required by this view, the few experiments have not given entirely concordant results, and it has been objected that the factor of intensity was not properly considered. It would be desirable to have this work repeated under carefully controlled conditions.

Non-resonance Hypothesis of Ewald.—Ewald, chiefly on the basis of ingenious experiments with artificial membranes of the minute dimensions of the basilar membrane (31 mm. long by 0.2 mm. wide at base and 0.36 mm. at apex), considered that the entire basilar membrane is thrown into standing waves, the pattern of which differs for different frequencies. This view is, however, hard to align with certain facts of sensation, particularly volume, and with the result of experimental injuries to the cochlea and has not proved fruitful.

Non-resonance Hypothesis of Roaf and Fletcher. Another hypothesis of the non-resonance type is that proposed by Roaf and adopted and extended by Fletcher, although derived from earlier workers. According to this view, the waves of low frequency, for example, below 20, find less resistance in their passage up the scala vestibuli and through the helocotrema than in displacing the membranes. As the rate is increased, the inertia of the liquid opposes its rapid transference over this long path and relief for the pressure is found by displacement of the wider and more flexible portion of the basilar membrane near the helicotrema. For any frequency the point of maximum displacement of the basilar membrane will occur at a spot where the inertia of the lymph and the flexibility of the

basilar membrane are properly balanced, which will be near the apex of the cochlea for the low frequencies and near the base for high. *Pitch* is thus dependent upon the portion of the series of hair cells stimulated; in this and in the position within the cochlea of these regions it is in agreement with the hypothesis of Helmholtz; it differs, however, in that the physical basis of vibration at these points is not resonance. *Intensity* is supposed to result from the amplitude of vibration of the basilar membrane and by implication, though not directly stated, upon the number of hair cells stimulated, since the vibrating zone is wider the greater the amplitude. It is also claimed that for loud, pure tones not only one region but several, corresponding to harmonics, are thrown into vibration by the mechanism of transmission of the ear. *Volume* is not specifically considered. *Analysis* is possible because for each element of the compound tone a maximum occurs on the basilar membrane. *Combination tones* and *masking* are accounted for by the interplay of the secondary maxima mentioned above. The presence of *tone lacunæ*, or *islands*, would receive the same explanation as in the hypothesis of Helmholtz, the presence of defective portions in the organ of Corti. The results of experimental injury are, as stated above, indecisive.

Comparison of the Number of Sensations with the Number of Known Structures.—The hypothesis of Helmholtz and of Roaf and Fletcher agree in assigning pitch to a particular locality in the organ of Corti and apparently in assigning intensity to the number of neurons stimulated. Neglecting volume, on which data are scanty, it is interesting to see whether the known anatomical structures can reasonably account for the observed sensations. It has been estimated that at the most favorable amplitudes about 1500 pitches can be distinguished and that at medium frequencies a maximum of about 270 steps of intensity, or a total of somewhat over 300,000 sensations. There are known to be slightly over 15,000 hair cells and about 14,000 nerve fibers in the cochlear nerve, a number about one-twentieth that of the sensations for which we must account. It is clear that each neuron must appear more than once in various combinations if these hypotheses are correct in principle.

If we assign to each pitch a section of the organ of Corti the unit in which this will have to be measured is that of a transverse row of hair cells. Such a row includes in most of the cochlea 5 hair cells, and since there are about 15,000 hair cells there would be 3000 or somewhat less of these rows. Since there are 1500 pitch steps to be accounted for, each step might be assigned two rows of hair cells. We find, however, that intensity discrimination is best at moderate frequencies and it might be imagined that here more than two rows corresponded to one pitch, for example, four rows, while

toward the upper and lower ends of the basilar membrane there might be but a single row.

If we assume that at each pitch 200 intensity steps must be accounted for, a figure below the maximum but above the average, this would require 200 hair cells, or 40 rows of 5 each. Since we have assigned 4 rows to 1 pitch step in the central region, this would involve 10 pitch steps; that is, for the greatest amplitudes not only the 4 rows assigned to that pitch but about $4\frac{1}{2}$ groups of 4 rows each on either side are also called into play.

This might seem inconsistent with the sharpness of pitch and the delicacy of pitch discrimination, but two facts must be held in mind. In the first place, the pitch step here considered is an extremely minute one, to be discriminated only under carefully controlled experimental conditions, certainly not at the greatest amplitudes. For comparison it may be noted that in the region of best pitch discrimination (c^3, 1024, to c^4, 2048) the difference between successive tones represents on the average 160 vibrations and the quarter tone, the smallest step considered in music, corresponds to 40 vibrations. The pitch step used in the above calculations is, at this frequency, but a single vibration or one-fortieth of a quarter tone. The spread for the greatest amplitudes would thus be only one-sixteenth of a tone, a difference not noticeable under ordinary circumstances.

In the second place localization in the skin may be definite, although a number of receptors are involved; thus the points of the compass in the two-point test may be distinguished with accuracy, although each may be affecting 50 to 100 touch spots and the two depressions with their zones of stimulation may fuse into a single area. The localization is apparently on the basis of the point of maximum stimulation or the center of gravity of all the points stimulated and does not shift with changes of pressure. In the ear where the stimulation is also mechanical a similar pitch localization by maximal stimulation might reasonably be expected.

It seems, therefore, not impossible to account for the known sensations on the basis of known structures, if we assume pitch to depend upon the place in the cochlea and intensity upon the number of fibers stimulated.

Non-resonance Frequency Hypothesis.—As an example of a different view of cochlea function, the suggestions, as he calls them, of Boring regarding a non-resonance frequency hypothesis may be cited. He considers that, corresponding to the amplitude of the vibration, a greater or less extent of the organ of Corti, beginning at the base of the cochlea, is displaced, and therefore a greater or less number of fibers are stimulated, on which physiological basis rests *intensity*. *Volume* varies primarily, he thinks, with intensity,

and hence also rests in some way on the number of fibers. *Pitch*, therefore, must depend upon the number of impulses per second over the fibers. Here a problem is presented by the refractory period of the nerve. Values for the refractory period of mammalian nerve may be as small as 1.0 σ and 0.43 σ, corresponding to frequencies of 1000 and 2325. To account for the highest rate perceived, 20,000, the refractory period would have to be 0.05 σ. He considers it not impossible that the auditory nerve has a refractory period of this order of magnitude and that this point should be tested. *Analysis* he considers the most serious difficulty to such a frequency hypothesis, but makes no suggestions regarding this or regarding *combination tones*. The facts of localization are consistently explained by this view.

It is quite clear that while such diverse hypotheses hold the field the need is for further information rather than more theorizing, and the recent important experimental work on hearing gives promise that before long the data may be available.

Summary.

The ear is an extremely delicate and complex *distance receptor* for *mechanical stimuli*. The type of ear present in man is found only in the *higher land vertebrates*.

Longitudinal vibrations of the air or *sound waves* constitute the normal *stimulus* for the ear. Important facts concerning the *physical nature of sound* are the following: *Simple sounds* or tones, consisting of one frequency only although most readily treated mathematically, are difficult to produce experimentally. They may vary in *frequency* and in *amplitude*. *Complex sounds* or tones of two to many frequencies are produced by all musical instruments, the voice and other common sources of sound with which the ear deals. While the sensation of pitch aroused by a complex sound is named from the fundamental or lowest frequency, there are present a varying number of overtones of different intensities, depending on the source. On the *number* and *relative prominence of these overtones* depends the character or *timbre* of the complex sound.

The ear may be divided into *essential receptors* or *hair cells* of the organ of Corti and *accessory structures*, which include *sound-receiving, sound-conducting* and *converting*, and *sound-analyzing* structures. Sound is received by the *pinna* and *external auditory meatus, conducted* through the middle ear and *converted* from air to water waves by the *tympanic membrane, ossicles* and associated structures, and delivered to the *endolymph* of the inner ear containing the *hair cells* and *analyzing* structures.

The *reactions* initiated by the ear are chiefly of the complex *anticipatory* type found in other distance receptors. The *sensations* are

extraordinarily rich and varied. The attributes of simple tones are *intensity, pitch, volume* and *duration*. In addition, *complex tones* differ in *timbre*. Any tone has a *position in time* and *in space* (*localization*). The *intensity* of simple tones varies with the *amplitude* (or perhaps with the total energy) and also with the frequency. The *threshold* is least for frequencies of c^4 (2048) to c^5 (4096). With increased amplitude the intensity increases until cutaneous receptors are said to be involved. The functional range of intensity between the threshold and the upper limit of tolerance is greatest at moderate frequencies (512 to 1024) and is rapidly restricted in passing to lower or higher frequencies until below about 20 and above about 20,000 no pure auditory sensations are possible and the functional range of frequency is exceeded. The *discrimination of intensity* is keenest at moderate frequencies and at moderate intensities. The *pitch* of simple sounds varies with the frequency of the stimulus. The *discrimination of pitch* (expressed as a ratio between the detected change in number of vibrations and the frequency) is keenest at moderate frequencies and at moderate intensities. The *volume* varies with the amplitude and with the frequency, though not in the same way as do intensity and pitch. *Complex tones* differ in *timbre*. Two simultaneous tones (giving rise to a complex tone) may react on each other in three ways: They may *fuse*, or combine in an intimate fashion; they may develop *combination tones* representing frequencies not present in either; one may *reduce* or *mask* the apparent intensity of the other. *Fusion*, of great importance in music, occurs readily between frequencies in simple numerical relations as 1 to 2 (the octave) but less readily in more complex relations, such as 15 to 16, which are considered discords. Frequencies differing slightly give rise to *beats;* if differing more widely, to *combination tones*, including *difference tones* (with a frequency corresponding to the difference between the combining frequencies) and *summation tones* (with frequencies corresponding to the sum of the combining frequencies). Of two component tones, the higher is reduced in intensity, or *masked*. Sounds heard by both ears are *localized* with accuracy. Such *binaural localization* depends upon differences in *intensity*, in *time* and in *phase* of sound from the same source incident in the two ears.

The human *voice* is the sound to which the ear is presumably adapted. Here the tones are produced by the vibration of the free edges of the *vocal cords* of the larynx and *resonated* by the mouth and adjacent cavities. The range of the singing voice is from F_1 (42) to c^4 (2048). Above the fundamental of the higher note are approximately three octaves of overtones. The energy of speech is greatest at low frequencies, half lying below about 400, but the important region for the recognition of speech lies between 500 and

4000. There is a close correlation between the capacities of the ear and the range of sounds encountered in speech and music.

Cochlear function has been treated by numerous discordant hypotheses, convincing proof of our lack of accurate knowledge of its action. The following are representative examples of these hypotheses. The *resonance* hypothesis of Helmholtz assumes the presence of a series of *resonators* which are identified with parts of the *basilar* (or of the tectorial) *membrane*. *Pitch* depends upon the stimulation of a particular portion of the series of hair cells associated with the resonating section of the basilar membrane, and complex tones are analyzed because all involved resonators are simultaneously active. *Intensity* must apparently depend upon the *number of hair cells stimulated*. *Volume* has not been specifically accounted for. *Ewald* has proposed a *non-resonance* hypothesis, which assumes that the basilar membrane is thrown into standing waves, the pattern of which differs for different frequencies. It is difficult on this hypothesis to account for the other features of the sensations. *Roaf* and later *Fletcher* have advocated a non-resonance hypothesis. According to this, low frequencies affect part of the basilar membrane near the apex of the cochlea and high frequencies a part near the base, but not because of resonance. *Pitch* is thus dependent on the *portion of the series of hair cells stimulated* (as in the view of Helmholtz, but for a different reason). *Intensity* is supposed to result from the *amplitude* of the movement of the basilar membrane. *Volume* is not accounted for. A comparison of the *number of sensations* and the *number of structures* of the cochlea indicates that an explanation along the lines of Helmholtz or Roaf is possible. *Boring* has recently suggested certain features of a non-resonance *frequency* hypothesis. *Pitch* is supposed to rest upon the *number of impulses received per second*. *Intensity* depends upon the *number* of *hair cells* excited and *volume* probably in some way has the same basis

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CHAPTER XXXV.

VISION: IMAGE FORMATION.

The eye in man and the higher vertebrates represents probably the most highly specialized receptor, taking as a criterion either the complexity and delicacy of the accessory apparatus or the variety and fine shadings of the visual sensations. It must be remembered, however, that light-sensitive structures or tissues are present in an extremely simple form in many organisms. The eye is the chief distance receptor in man and the other primates and in birds, and sight is for them the dominant sense, replacing smell, which is so important in most mammals, and in certain respects surpassing hearing. In birds this is associated with their arboreal or aërial life. Odors cling to the earth or grass, particularly if moist, whereas no such trail can be left in the air that a bird might follow. The vision of ground-living birds, it appears, is below that of birds more given to flight. Collins has claimed that in man and the primates the development of vision is correlated with arboreal habits and probably with man's erect posture. Characteristic features of the human eye in which it excels that of most other animals are the fovea and the positions of the orbits, permitting binocular vision. The fovea, a portion of the retina specialized for distinct vision, is found in many birds, but here the orbits usually diverge so that the eyes do not have a large common field; a true fovea is absent from mammals below the primates and the orbits commonly diverge in varying degrees.

Sight most truly merits the term of distance sense, for smell and hearing at best can receive stimuli from sources distant but a few miles, whereas the eye can see the fixed stars millions of miles away; in fact, the eye is the only one of the receptors, excepting the warm spots, capable of being affected by stimuli originating outside of the earth.

The highly developed accessory apparatus of the eye deals chiefly with the direction of the stimulating object; its utility, upon which rests this dominant position of sight, depends on the regularity and predictability of the propagation of light.

If light did not travel in "straight lines," but, like odors, was transported by capricious air currents or like sound, which, though more regular than odors in its transmission, is yet affected by winds, and because of its great wave length bends when it passes

around corners, the accessory apparatus of the eye would be practically useless.

The reactions initiated by the eye are of the same type as those associated with the other distance receptors, precurrent reactions, such as locomotion, leading up to various consummatory reflexes. It is notable that, because of the long distance over which its stimuli may be carried, it affords a longer interval of preparation than does any other receptor, and thus comes to play a correspondingly significant part in the development of the more flexible behavior of the higher organisms. This relation is reflected in the regard in which sight has always been held by man. It is interesting that nearly all of our instruments of precision depend upon the eye - microscopes, telescopes, spectroscopes, balances, thermometers, chronometers, barometers and in general all instruments using scales. On the other hand, most means of communication, telegraph, telephone, radio and the like, depend upon the ear, although through printing devices they may also appeal to the eye.

THE STIMULUS.

Light or radiant energy, or more exactly *visible radiation, as the stimulus for the eye,* presents two features requiring careful consideration. In the first place, the radiation absorbed by a body has the power of causing, under appropriate conditions, photochemical or photo-electrical changes. These conditions are found in certain living tissues and constitute the basis of reactions to light by animals and plants and of the important energy transformation involved in photo-synthesis in plants. The stimulation of the retina belongs to this category and requires for its understanding a knowledge of the photo-chemistry of light. In the second place, the propagation of radiant energy is affected by its passage from medium to medium in such a way that images may be formed. A large part of the accessory apparatus is devoted to image formation.

To follow image formation and retinal stimulation in the eye we must have before us the essential features of its structure.

ANATOMICAL BASIS OF IMAGE FORMATION.

Comparative Anatomy of Light-sensitive Structures.—The anatomy of the human eye is so complex that its essential features may profitably be prefaced by a brief survey of some of the simpler light-sensitive structures. Light-sensitive tissues which yet show no visible structural differentiation are known in a number of organisms. These are cases in which the physico-chemical constitution of some element of the cells makes possible photo-chemical changes

and, therefore, an alteration of the functional metabolism. This represents the simplest form of light-receptive structures; it is illustrated by the skin of the earthworm, the tube feet of the starfish and the excised iris of some eyes. The simplest recognizable organ consists of a light-sensitive cell or cells in association with insensitive accessory cells which serve to exclude, reflect or refract the light. By such means the effect of sources of radiant energy in different positions is rendered different and a basis furnished not only for reactions to light but for differential reactions to lights in varying relations to the organism.

From this simple beginning of a light-sensitive surface we may trace through a series of selected animals the steps leading to the highly developed eye of man. The complications of the photosensitive surface have followed two directions. In one the surface has become convex; this plan of organization, which culminates in the insect eye, throws no light on the vertebrate type and will not be considered here. In the other the surface has become concave; to this type belong our own eyes. One of the simplest forms is the optic pit in which the sensitive cells occupy the bottom of a depression of the body epithelium; such pits are found in limpets and other simple mollusks. It is clear that light will reach the sensitive cells most readily in a direction perpendicular to the body surface, whereas from oblique directions the margins of the pit will reduce its intensity or exclude it completely. Such a receptor has been called a *direction eye*. The pit type may show a modification in which the opening is much smaller than the depth of the pit and the sensitive layer extends over the greater part of the spherical interior. Light from a variety of directions may enter such an eye, but that from each direction will fall upon a different portion of the sensitive lining, the conditions being those for the formation of a pinhole image. This is the simplest *image-forming* eye. The interior of a pit may, on the other hand, be filled with transparent cells which transmit the light and also because of their shape act as a lens and produce a lens image. This will allow the entry of more light than the pinhole type and thus forms a more useful image.

It is clear that the significant features of an eye of this type are: (1) An *essential photo-chemical receptive surface;* (2) an *optical device by which light from a particular external source is made to fall upon a particular portion of the light-sensitive surface.*

STRUCTURE OF THE HUMAN EYE.

We will now consider briefly the anatomy of the human eye, after which it will be possible to present the plan of treatment of its functions which will occupy this and the succeeding chapter. The

visual organ consists of a bulb containing a layer of photo-sensitive cells and the accessory apparatus required for the formation of images on this sensitive layer, and attached to this bulb the muscular mechanism accomplishing the many accurate movements involved in vision. In addition, there are means of maintaining the nutrition of the bulb and insuring the protection of an organ that is necessarily placed in a prominent position.

The Orbits and Their Contents.—The eyes are lodged in two orbits of pyramidal shape, with their apices directed toward the center of the skull and lying nearer together than the centers of their external bases, a situation conditioning the ocular movements and protecting the bulbs from mechanical stimulation or injury. Besides the eye the orbit contains the extrinsic ocular muscles

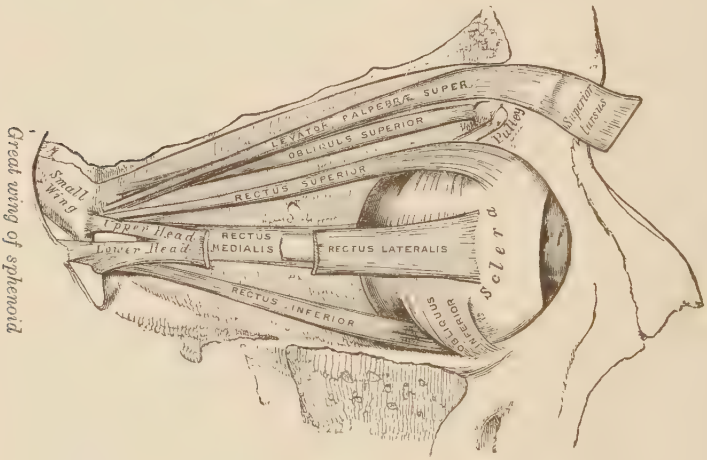

Fig. 78.—Muscles of the right orbit from the side. (Cunningham.) The orbital fat has been removed. (Gray's Anatomy, Lea & Febiger, Publishers.)

and the lid muscles, the lachrymal gland, the bloodvessels and a considerable mass of orbital fat imbedded in loose connective tissue. The bulb thus lies half enclosed in a cup-like depression in the pad of orbital fat in which it rotates after the manner of a ball and socket joint. The actual movement takes place between the globe and a tunic of fascia, the fascia bulbi (capsule of Tenon), the space containing a lubricating fluid, as does a synovial cavity.

The extrinsic ocular muscles, six in number, pass from the eyeball to the wall of the orbit. The four recti (superior, medial, inferior and lateral) have their origin near the apex of the orbit and run forward to insertions in the bulb somewhat in front of its equator on the aspects indicated by their names (Fig. 78). The superior oblique originates with the recti, runs forward in the superior-medial

part of the orbit, passes through a fibro-cartilaginous ring or pulley, turning an angle with its former course of somewhat less than a right angle and attaches to the superior surface of the bulb. The inferior oblique unlike the others takes origin from the inferior-medial wall of the orbit near its front and passes laterally and more deeply into the orbit to be inserted in the lower surface of the bulb.

The tendons of these muscles perforate the fascia bulbi and thickenings of the latter pass from the four recti to the margins of the orbit, forming the *check ligaments*. The bulb thus lies pressed into a cup of fat by the tonic contraction of the recti muscles and free to rotate within limits about any axis. Movements into the orbit are opposed by the incompressible orbital fat and out of the orbit by the tone of the muscles; gradual protrusion or recession, however, may occur from changes in the amount of blood in the orbital vessels or in the amount of orbital fat. Lateral movements are opposed by the orbital fat and the check ligaments, but in general the orbit protects the eye from pressures which would mechanically shift its position. The varied and delicate movements of the eyes actually carried out will be considered in Chapter XXXVI, page 664.

Protection is furnished the eye by the *lids* and their *lashes* and by the *tears* which flow over the front of the bulb. Not only do the tears have an important protective function in removing irritating particles, but, as we shall see, they form the first optical surface for entering light.

The Structure of the Bulb.—The eye consists of three concentric coats and of certain liquid and solid parts enclosed by them. These coats are: (1) The outer *fibrous tunic* (*sclera* and *cornea*); (2) the middle pigmented and in part muscular *vascular tunic* (*chorioid*, *ciliary body* and *iris*); (3) the inner nervous *retina*. Within these coats are enclosed the *vitreous body*, the *crystalline lens* and the *aqueous humor* (Fig. 79).

The *fibrous tunic* gives form and strength to the bulb, since it is relatively inextensible and under a constant tension from the liquid contents which exert an *intra-ocular pressure* of about 26 mm. of mercury. The antero-posterior or sagittal diameter of the bulb is about 24 mm., its transverse diameter somewhat more (24.5 mm.) and its vertical diameter rather less (23.5 mm.) -these values vary apparently with the size of the person and also with errors of refraction which may be present. The *sclera*, or *white of the eye*, forms the greater part of the fibrous tunic; its most significant features are its firm texture due to a large amount of white connective tissue and its opacity to light. Anteriorly, the sclerotic coat is completed by the transparent *cornea* representing a portion of a smaller sphere with a radius of about 8 mm. instead of 12 mm., as shown by the sclera. The curvature is usually somewhat greater in the vertical than in the horizontal meridian corresponding to a difference in the

vertical and horizontal diameters of the cornea and to a similar difference in the diameters of the bulb noted above.

The cornea, like the sclera, is composed essentially of strong connective-tissue fibers, but so modified that they and the contained liquid present so nearly the same index of refraction as to appear

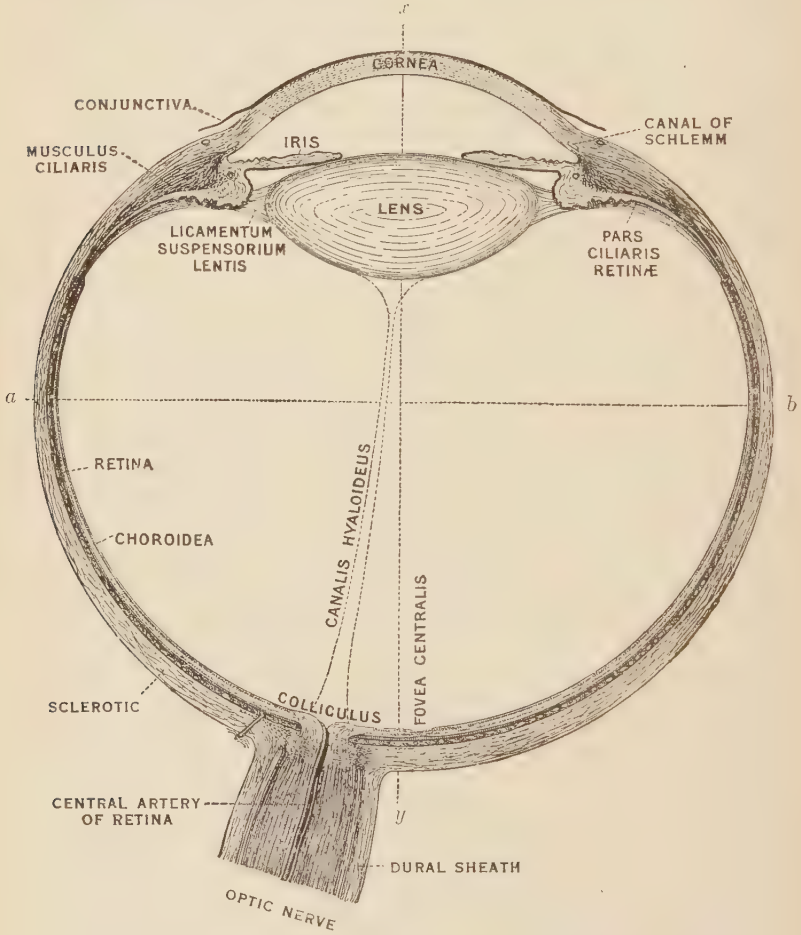

FIG. 79.—Right adult human eye nearly horizontal section. The line x—y marks the optic axis of the eye, a—b, the equator. (From Schäfer's "Essentials of Histology," by permission of the author.)

completely transparent and optically homogeneous. Anteriorly, the cornea is covered by an epithelium continuous with the conjunctiva lining the lids. (For other features of this or other parts of the eye not here considered, a standard text book of anatomy or histology should be consulted.)

Vascular Tunic.—Unlike the fibrous, the vascular tunic does not from a complete layer; posteriorly the *chorioid* lies between the sclera and the retina, as does its forward continuation, the *ciliary body*, but the *iris*, arising from the ciliary body at about the junction of sclera and cornea, lies freely in the space between the cornea and the lens, though normally in contact with the latter. The incompleteness of this coat results from the perforation of the iris by the approximately central *pupil*. The *chorioid* is notable for the great number of bloodvessels and abundant pigment; in fact, it consists of little beyond these and a small amount of connective tissue binding them together. Anteriorly this passes into the *ciliary body*, which is much thicker and quite different in structure. The two most important features are the radial folds, or *ciliary processes*, on the inner surface and the *ciliary muscle* imbedded in the deeper parts. The ciliary processes, which are covered by a thin prolongation of the retinal layer, present a large surface and are considered to have a secretory function.

The *ciliary muscle* consists of a ring of smooth muscle fibers triangular in cross-section lying next the sclera. Its fibers have two courses: Part take origin from the sclera near its junction with the cornea, pass radially back and out to insert in the chorioid; other fibers lying near the inner surface and close to the base of the iris take a circular course. The action of the ciliary muscle will be considered in discussing accommodation (page 608).

The *iris* consists of a delicate connective-tissue framework, or *stroma*, containing numerous bloodvessels, smooth muscle fibers and, in the dark-colored irides, varying amounts of brown pigment. In all non-albinic eyes the posterior surface is covered with a layer of black pigment cells derived from the retinal layer, and it is to this pigment seen through the stroma that gray and blue eyes owe their color. The smooth muscle fibers of the iris are disposed in two ways; part are arranged circularly near the posterior surface at the pupillary margin forming the *sphincter*; part take a radial course just beneath the posterior pigment layer forming the *dilator*.

The Retina.—The *retina*, like the vascular tunic, forms an incomplete coat. It lines the posterior part of the bulb and extends forward to the margin of the pupil; before the *ciliary body* is reached, however, it undergoes an abrupt transition at a point marked on the inner surface by a wavy line, the *ora serrata*. Anterior to this it is markedly thinner and differs both structurally and functionally from the posterior portion, to which the term retina is, in practice, restricted. Other regional differences will be considered when the function of the retina is discussed (page 628).

Because of their origin the retina and the optic nerve should be considered as part of the brain (page 587); the optic nerve is not homologous with the other cranial nerves but with a tract of the

brain. In the adult the retina forms a complex coat in which at least ten layers can be distinguished, although it is less than 0.5 mm. thick. Essentially it consists, beginning at the chorioidal surface, of a pigment layer and a series of three neurons with supporting cells. The first, or outer layer of neurons, which it will be noted is that last reached by entering light, consists of elongated cylindrical cells of two types, called because of their shapes *rods* and *cones*. These communicate by synapses with the *bipolar cells*, which in turn communicate with the *ganglion cells*, the axons of which constitute the optic nerve (Fig. 80). (Further details will be given later, page 631.)

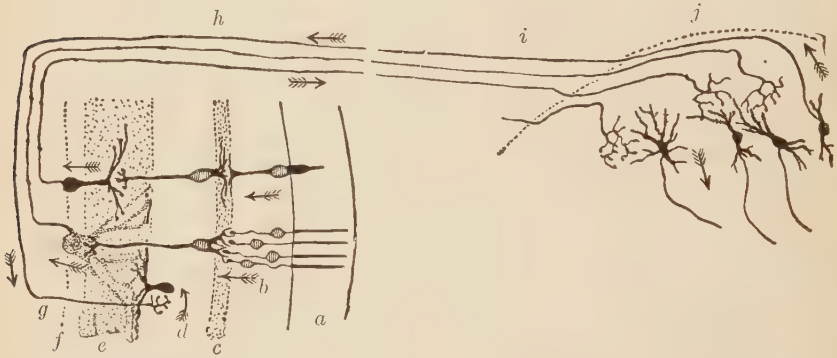

FIG. 80.—Diagram of the connection of the retinal elements with one another and with the central nervous system. (Cajal.) *a*, rod and cone layer; *b*, outer nuclear; *c*, outer molecular; *d*, inner nuclear; *e*, inner molecular; *f*, ganglion cell giving rise to fiber of optic nerve; *g*, *h*, *i*, a centrifugally conducting fiber arising from a cell in the brain and with its terminal arborization in the retina; *j*, gray matter of corpus quadrigeminum. (From Schäfer's "Essentials of Histology," by permission of the author.)

Vitreous Body.—The greater portion of the bulb within the retina is filled by the *vitreous body* (or vitreous humor), consisting of a delicate stroma of fibers covered by the hyaloid membrane and filled with a liquid, which constitutes most of its bulk. This liquid is the same in origin and composition as the aqueous humor.

Crystalline Lens.—The crystalline lens is a transparent biconvex body, 9 or 10 mm. in diameter and about 4 mm. thick. It lies in a depression in the front of the vitreous body, immediately behind the iris, where it is supported by the *suspensory ligament*, a structure closely associated with the hyaloid membrane, which passes from the ciliary processes to the equator of the lens. The lens is composed of many slender fibers arranged in concentric layers; in the fresh state the outer layers are soft and easily detached; the central portion, or *nucleus*, is more firm. The fibers are enclosed in an elastic *capsule*, to which the fibers of the suspensory ligament are attached. A normal lens appears transparent and homogeneous,

although, like the cornea, it consists of numerous fibers united by small amounts of cement and containing varying amounts of fluid. Despite the fact that there exist no obvious differences of optical density between adjacent lens elements which make them visible to direct observation, the lens is not homogeneous in this respect, but becomes progressively more refractive as we pass from the periphery to the center. This peculiarity, as well as the changes in accommodation occurring with age (page 612), result from the mode of growth of the lens. The central fibers are the oldest and throughout life new fibers are developing by the elongation of epithelial cells at the periphery. With age the fibers lose their nuclei and become smaller and more dense from loss of water. The shrinkage partially compensates for the increase in number of fibers, but there is a slow gain in bulk with age. As a result, the older central nucleus is both firmer and optically more dense, and with advancing age more and more of the lens takes on the character of the nucleus. Details of the shape and dimensions of the lens will be given in connection with accommodation (page 610).

Aqueous Humor.—The aqueous humor filling the cavity between the cornea and lens completes the contents of the bulb. It will be considered in connection with the nutrition of the eye (page 588).

DEVELOPMENT OF THE EYE.

Rudiments of the eye can be distinguished at a very early stage in man and other mammals. Before the neural tube has closed, outpocketings of the forebrain, the optic vesicles, appear on either side. The overlying ectoderm with which they soon come in contact thickens and invaginates, forming the *lens vesicles*, while at the same time the optic vesicles become indented and take a form justifying the term *optic cups*. They retain connection with the brain by the stalks which are destined to become the optic nerves. The inner thicker layer of the cup differentiates into the complex nervous and supporting elements of the retina, while the outer layer forms the pigment of the retinal coat. The lens vesicle becomes separated from the ectoderm and by the growth of the inner portion the cavity is obliterated and the lens ultimately formed. The vitreous body arises from a bud of mesoderm reaching the interior of the optic cup through the chorioidal cleft in the lower edge. The mesoderm surrounding the optic cup forms the chorioid and the sclera. In front the iris and the cornea also arise from mesoderm, being separated by a cleft that later becomes the anterior chamber. The iris is at first a continuous sheet in which the pupil appears shortly before birth. The growth of the eye closely parallels that of the brain. It is thus relatively far nearer its final size at birth than are most organs; the eye increases between three and fourfold in weight after birth, whereas the entire body increases over twenty-fold.

NUTRITION OF THE EYE.

The eye presents a problem of nutrition which deserves special consideration, both from its physiological interest and its relation to certain diseases of the eye. The vascular tunic receives from the posterior and anterior ciliary arteries a rich blood supply. The retina receives an adequate blood supply from an entirely separate source. The central artery entering with the optic nerve spreads over the inner surface and the blood leaves by the central vein; the capillaries, however, do not penetrate the rod and cone layer. The other structures traversed by light, the cornea, aqueous humor, lens and vitreous body, contain in the adult no bloodvessels. This represents the largest non-vascular mass in the body, thus presenting a peculiar problem of nutrition. Of course, the metabolism of these structures is not high, but it is clearly not absent, particularly in the lens, and the pathological opacity of cataract bears some relation to this situation.

We will first consider the liquid content of the bulb, since it is from this that the lens and the cornea receive their nourishment. The fluid filling the stroma of the vitreous is, as we have said, the same as that filling the aqueous chamber; communication between these two regions is possible through the fibers of the suspensory ligament and the pupil. This liquid is normally under a pressure of between 25 and 30 mm. of mercury, a pressure below that in the arteries but above that in the veins and approximating that in the capillaries. An abnormally low pressure would fail to maintain the proper relative position of the refracting surfaces; too high a pressure, such as is sometimes found in glaucoma in which arterial pressure is approached, interferes with the ocular circulation, and finally causes injury to the optic nerve.

The intra-ocular pressure depends upon the balance between the production and escape of the liquid contents of the eye. Although the details of the production and the escape are not satisfactorily known, the main facts appear to be these. The liquid which closely resembles lymph except for the absence of fibrinogen is apparently secreted by the ciliary processes and thence finds its way into the stroma of the vitreous body and by the route suggested above into the aqueous chamber. Part of the liquid apparently escapes from the bulb through the perivascular lymph spaces surrounding the retinal vessels. The greater portion, however, escapes in the region of the iris. Some is apparently taken up by the veins of the iris, but the more important route is through the spaces of Fontana, in the angle between the cornea and the base of the iris into the canal of Schlemm, which clearly communicates with veins in the sclera. The high pressure of glaucoma apparently arises from interference with the outflow rather than increased secretion.

The liquid in the interstices of the cornea and the lens must be replenished by diffusion from the aqueous. It is a curious fact, however, that if the capsule of the lens or the posterior elastic membrane (the membrane of Descemet) lining the cornea is scratched, and the aqueous finds direct entrance, it causes injury, swelling and if continued, in the case of the lens, ultimate destruction.

Although in the adult the slow process of diffusion serves to meet the needs of the low metabolism, there are occasions when this is supplemented. During the rapid growth of the lens in the fetus it has an abundant blood supply from the hyaloid artery arising from the central artery, and during the healing of injuries in the cornea vessels may invade a region usually non-vascular.

CLASSIFICATION OF STRUCTURES INVOLVED IN VISION AND PLAN OF TREATMENT.

We are now in a position to group the structures of the eye according to the part they play in vision. They may first be divided into: (*A*) *Essential receptors*, the retina, or, more exactly, the rods and cones; (*B*) *accessory structures*. The accessory structures comprise:

(*a*) An *image-forming* apparatus, including all parts contributing to the formation of images.

1. All *media traversed by light*, tears, cornea, aqueous lens, vitreous body and most of the retina.
2. Apparatus for *focussing*, including the lens, suspensory ligament, ciliary muscle.
3. *Light-excluding* structures, sclera and the pigments of chorioid, iris and retina.
4. *Light-regulating* apparatus, the iris (and migratory retinal pigment in certain animals).
5. Mechanism for *preserving position* of parts of *optical system*, sclera and intra-ocular pressure.

(*b*) *Directive apparatus*, orbital fat, muscles, fascia bulbi, check ligaments and associated structures.

(*c*) *Protective apparatus*, orbit, lids and lashes, eyebrows, lachrymal apparatus.

(*d*) *Nutritional apparatus*, structures involved in production and circulation of aqueous humor.

In addition, certain features of the central connections of the eye require consideration under this head.

The questions of protection and nutrition require no further treatment than that given above in connection with the structures. It will be convenient to treat the remainder in the following order: The *image-forming* apparatus, prefaced by an introduction to the necessary *physics of radiant energy* (comprising the remainder of

this chapter), the *essential receptors* and the *visual sensations,* and last, the *directive apparatus* and *binocular vision* (which will occupy Chapter XXXV).

REFRACTION AND IMAGE FORMATION.

Visible Radiation.—The stimulus for the retina consists of a small range, approximately one octave, of electromagnetic frequencies included in a spectrum which has now been carefully explored through about fifty octaves. The stimulating frequencies—*visible radiation*—do not all have equal effect, but present a sharp maximum at about 540 fresnels,[1] or, as more commonly expressed, at a wave length of 556 mμ.[2] in the yellow. As we pass in either direction the visibility decreases rapidly until it is but $\frac{1}{100}$ of the maximum at 429 mμ. and 687 mμ. and $\frac{1}{1000}$ at 408 mμ. and 720 mμ. The relative visibility of these frequencies is represented in Fig. 102. It is obvious that the visibility does not parallel the total energy of sunlight represented in the same figure.

It will be convenient to introduce at this point a few photometric definitions. *Luminous flux* is radiant energy evaluated according to its capacity for producing sensations of light (more exactly sensations of brilliance; page 636). The *international candle* is the unit of luminous intensity. The *illumination* on a surface is the flux density or the flux intercepted per unit area of that surface. The *lumen* is the luminous flux emitted in a unit solid angle by a point source of 1-candle power, or more simply the luminous flux intercepted by a unit area at a unit distance from such a source. The units of illumination in use are: The *lux*, or *meter candle*, 1 lumen per m.^{2} or the flux intercepted by 1 m.^{2} at 1 m.; the *phot*, 1 lumen per cm.^{2}; the *milliphot*, 0.001 phot; the *foot candle*, 1 lumen per ft.^{2},

1 mph. = 0.001 ph. = 10 mc. = 0.929 ft. c.

The *brightness* of a surface is the luminous intensity per unit area. The units are: The *lambert*, 1 lumen per cm.^{2} (the brightness of an ideal surface reflecting all of the light when illuminated by 1 phot) and the *millilambert*, 0.001 lambert.

Because the visual effect is restricted to this small region we need not in our treatment of image formation consider the physics of any other portion of the electromagnetic spectrum, although it apparently shows throughout a similar behavior.

[1] One fresnel = 1 vibration per 10^{-12} second.

[2] Wave lengths are usually expressed in *millimicrons* (1 mμ = 1 × 10^{-6} mm.) or in *Ångstroms* (1 Å = 1 × 10^{-7} mm.). It would be preferable to designate visible radiation by frequency as we do sound, rather than wave lengths, since the frequency is constant whereas the wave length varies (page 591). Custom has, however, sanctioned wave length, which must be understood as that *in vacuo*.

The objects, or, in a less rigid sense, the stimuli, for vision include not only luminous and reflecting bodies but also real optical images (but not virtual images). The objects, in short, may be actual sources of light or merely points of departure; these can be defined as *configurations of points emitting visible radiation.* Since the physiological effects of different parts of the visible spectrum are not the same, the source of radiation is not a matter of indifference. Most sources are bodies at high temperatures; examples are the sun and the fixed stars (the moon and the planets merely reflect), matter heated by a flame (the fine carbon of the candle flame or the mantle of a gas lamp) or wires heated by the passage of an electric current (incandescent lamp). Such heated bodies give off radiation not only in the visible range but also in neighboring regions; the relative intensity of the different frequencies varies with the temperature, and hence the resulting sensations differ. Sunlight is our ordinary standard; it contains all visible frequencies in a proportion that we accept as "white" light. The temperature of the sun is about 6500° K. (K., absolute temperature, = Centigrade + 273°), but because of absorption by the earth's atmosphere the distribution of visible radiation is approximately that of a source at 5000° K. At lower temperatures the longer wave lengths predominate and the light is judged to be yellow as that of a candle flame, or red as that of a heated bar of iron, at higher temperatures the shorter wave lengths predominate and the color is bluish.

The electromagnetic waves that constitute light are transmitted through space as vibrations transverse to the direction of propagation at the immense velocity of 300,000 km., or 186,000 miles (the latest exact determination for air is 299,796 km.) per second, and through appropriate or *transparent* media at velocities slightly less.[1] If we imagine a very small source suddenly to become luminous the disturbance will spread with equal rapidity in all directions and at any instant its wave front will form a spherical shell. Its mode of propagation is so regular and predictable that its study constitutes an entire branch of physics called geometrical optics. The methods found most convenient in tracing the path of light are not necessarily applicable to other problems; this is particularly true of the method involving the conception of a *ray* of light. A ray may be thought of as a very small beam, such as might be admitted to a darkened room through a pinhole in a blind; actually

[1] In consequence of these differences of velocity, the wave length is different in different media. Velocity (V), wave length (λ) and frequency (n) have the following relation: $V = n\lambda$. Since n is constant, it is clear that the wave length must change with every change in velocity. Light reaching the retina through the media of the eye does not have the wave lengths in which the spectroscope is calibrated. For these reasons frequencies, rather than the customary wave lengths should logically be used in defining the type of radiation.

the attempt to isolate any such "element" of light gives rise to complications, so that it is best to regard a "ray" as a geometrical fiction corresponding to one of the radii of a spherical wave front, or, in general, simply a perpendicular to the wave front, at the point under consideration.

Visible radiation emanating from a source meets with various fates when it encounters various bodies. It is propagated through space, whereas sound is not, through most gases, as, for example, air, through a number of liquids, as water, and through a limited number of solids, as glass, quartz and calcite. Visible radiation traversing a medium and encountering a body may be *transmitted*, and in so doing usually changed from its course or *refracted*, it may be *absorbed* or *reflected* or it may suffer in part all three fates.

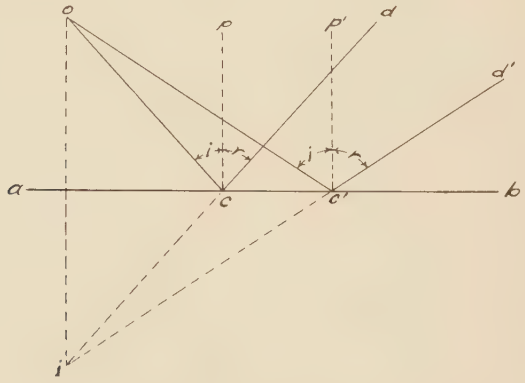

Fig. 81.—Reflection at a plane surface. See text.

The portion absorbed is changed to some other form of energy, usually heat, or, in the case of the retina, apparently chemical energy. Most transparent bodies, such as glass, absorb part of the light. Often the absorption is selective, that is, certain wave lengths are absorbed in greater degree than others, and the remainder, which is transmitted or reflected, differs from the total incident light in composition, and therefore in the sensation which it produces. It is to this fact that objects owe their color; a red flower is red because other wave lengths are absorbed and only those giving the sensation of red are reflected; a copper sulphate solution is blue because only the wave lengths causing the sensation of blue are transmitted, all others being absorbed. Such bodies as absorb the greater part of all wave lengths are considered "black."

Reflection.—The results of reflection differ with the surface; if this is irregular as that of blotting paper the light is given off in all directions and the reflection is said to be *diffuse* or irregular;

if the surface is smooth as that of polished metal mirrors the reflection is said to be regular. In the latter case the reflection occurs in certain definite directions dependent upon the previous course of the light, hence we see objects "in" a mirror as through the air. The way in which the direction is changed may readily be illustrated. If *ab* (Fig. 81) represents the trace of a reflecting surface on the paper, and *oc* an incident ray of light from the point source *o*, making with the perpendicular *pc* the angle *i* (the angle of incidence), the reflected ray will lie in the plane determined by *oc* and *pc* at an angle *r* (the angle of reflection) equal to angle *i*. Light reaching the eye will appear to come from a point lying behind the mirror on the prolongation of *dc*. If a second ray striking the mirror at a second point *c'* is similarly treated it will be found apparently to come from a point on the prolongation of *d'c'*. A point *i* at the intersection of *dc* and *d'c'* will thus appear to be the source of the light reaching the eye, and is called the image of *o*. It will readily be seen that *i* lies on the perpendicular from *o* through *ab* and as far behind the surface as *o* is in front of it. Other cases of reflection need not be considered here.

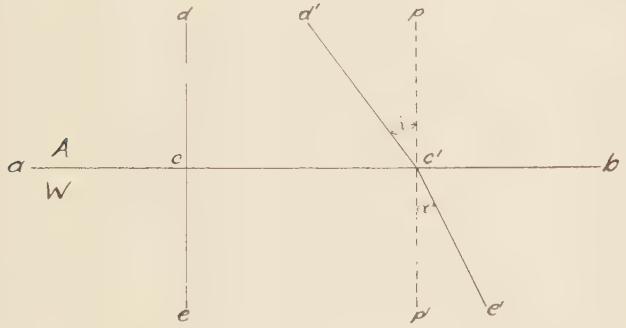

FIG. 82.—Refraction at a plane surface, ray method. See text.

Refraction.—Refraction as a more important phenomenon in vision must now be considered. When visible radiation passes from one transparent medium into another the velocity and the course are usually changed. The course of the radiation may be followed by two methods, by tracing the *ray* or by determining the modifications of the *wave front*. Let us consider two of the simplest cases, first by the more common ray method and then by the method of wave fronts.

Let *ab* (Fig. 82) represent the trace of the surface separating air (*A*) from water (*W*) and *dc* a ray in air perpendicular to *ab* at *c*. In water its course will be *ce*, a continuation of *dc;* the ray is undeflected, although, as we shall see, it suffers other changes. In the

second case let, as before, $d'c'$ represent the incident ray which makes with the perpendicular pc' the angle i (this is the angle of incidence; in the case above the angle of incidence was 0). The course of the ray in the water will be found not to be the same a in the air. It will, as did the reflected ray, lie in a plane determined by the incident ray $d'c'$ and the perpendicular $p'c'$, but will make with the latter an angle r, which in the present case will be less than angle i. In the case of the passage of a ray from air to water experimental determination of the angle of refraction for many angles of incidence shows that the ratio of the sine of the angle of incidence to the sine of the angle of refraction is a constant, with the approximate value of $\frac{4}{3}$.

$$\frac{\sin i}{\sin r} = \frac{4}{3}$$

This method is incomplete in that it shows no change in the case of the a ray entering the water perpendicular to the surface and in giving no clue to the reason for the observed relations between the angle of incidence and the angle of refraction.

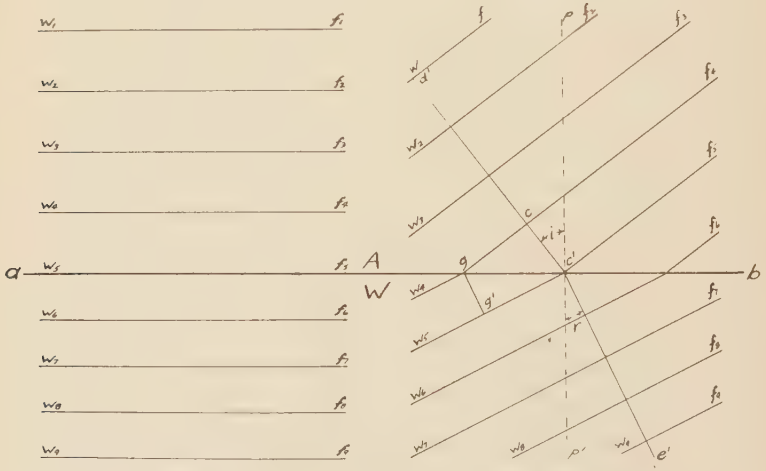

FIG. 83.—Refraction at a plane surface, wave-front method. See text.

Wave Front.—Let us apply to these two cases the wave-front method. If we imagine in the first case above a wave front of so large a sphere, that is, from so distant a source, that the portion with which we are concerned may be considered a plane parallel with the air-water surface, its fate may be more readily visualized. Through space it advances at the rate of 300,000 km. per second (through air its rate is but slightly less), so that at successive minute intervals of time the wave front may be represented by the parallel

lines, w_1f_1, w_2f_2, w_3f_3, etc. (Fig. 83). In other media, however, its velocity is less; in water it is approximasly 225,000 km. per second. This fact is often expressed by saying that water is optically more dense than air. After entering the water the progress of the wave front will be less rapid and in the time that it had advanced from w_4f_4 to w_5f_5 it would progress only $\frac{225{,}000}{300{,}000}$, or three-fourths as far, and the successive wave fronts would lie at w_6f_6, w_7f_7, etc. The wave fronts in water remain parallel to those in the air, which agrees with the fact noted above, that the ray suffered no deflection, but this method indicates the fact, which the previous one did not, that the velocity of the radiation has been reduced by a definite amount.

The conditions of the second case may now be realized by imagine ing that the wave front w_1f_1 is inclined to the surface ab, so that the angle of incidence is the same as above. If points g and c on wave front w_4f_4 are considered, it will be clear that during the time while c was moving to c', g would have advanced but three-fourths as far in the water and would lie at g'. If the positions of all points on the wave front are similarly developed they will be seen to lie along $c'g'$, and the next position of the wave front will be w_6f_6. If now the "rays" are drawn perpendicular to these wave fronts at the point c' we obtain the picture given above. The angle of incidence $pc'd'$ is less than the angle of refraction $p'c'e'$ because in entering the optically denser medium that portion of the wave front entering first has been retarded and thus the front as a whole assumes a direction more nearly parallel to the water surface.

It can also be shown that the ratio of the sine of the angle in the first medium to that of the sine of the angle in the second is equal to the ratio of the velocity of light in the first medium to the velocity in the second.

$$\frac{\text{sine angle incidence}}{\text{sine angle refraction}} = \frac{\text{velocity in air}}{\text{velocity in water}}$$

Angle cgc' = angle $pc'd'$, angle of incidence and similarly angle $gc'g'$ = angle $p'c'e'$, angle of refraction, since in each case the angles in question are complementary to the same angle. Now the ratio of $\frac{cc'}{gc'}$, the sine of angle cgc', to $\frac{gg'}{gc'}$, the sine of angle $gc'g'$, or

$$\frac{\frac{cc'}{gc'}}{\frac{gg'}{gc'}} = \frac{cc'}{gg'}$$

which by construction is the ratio, $\frac{\text{velocity in air}}{\text{velocity in water}}$.

Thus the ratio of the sines is the ratio of the velocities.

It should be noted that if the direction of propagation is reversed, and the light passes from the water into the air, all the relations diagrammed will still hold; the terms incidence and refraction will merely be interchanged. The wave front in passing from the optically less dense to the more dense medium is rotated, so as to lie more nearly parallel with the surface and *vice versa*. Or, expressed in terms of the ray, light is refracted toward the perpendicular in passing from a less dense into a more dense medium or away from the perpendicular in passing from a more dense into a less dense medium.

The ratio of the sines of the angles or of the velocities in any case is known as the relative index of refraction. It is customary to compare any medium with a vacuum or (without appreciable error) with air and to call this the *absolute index of refraction* or simply the *index of refraction*. Since the light is supposed to pass from the vacuum into the medium in question, and since the velocities in all media are less than in vacuum, this ratio is always greater than unity:

$$\frac{\text{velocity in vacuum}}{\text{velocity in water}} = \frac{300{,}000}{225{,}000} = \frac{4}{3} = 1.33.$$

The value for glass varies with its composition, but is roughly $\frac{3}{2}$, or 1.5.

The wave front may, however, be treated in a different manner. Light from a point source in a homogeneous medium presents a wave front determined by the distance and direction of the point from the surface at which refraction is to be considered. The form of the wave front is so important in determining its behavior that the following relations should be kept in mind. The *curvature* of the wave front, which may be defined as the *change of direction per unit length of arc*, is equal to the *reciprocal of the radius of the sphere*, $C = \frac{1}{r}$.

This may be shown as follows: The entire change of direction in a great circle of the sphere representing the wave front is equal to 2π radians, the total length of arc or circumference equals $2\pi r$. Dividing the change of direction by the length of arc we have $\frac{2\pi}{2\pi r}$, or $\frac{1}{r}$. This will clearly be true of any portion of the circumference or for any angular measure.

The wave front may be either convex or concave with respect to the direction of propagation of the light, that is, the light may be moving away from the center or toward the center of the sphere. These two conditions are distinguished by the sign of the curvature

which may be thus defined. The radius is a directed distance measured *from the surface* (or circumference) *toward the center; if the propagation of light is in this direction the curvature is positive.* The light is then advancing toward a center or the rays are *converging.* If on the other hand the direction of the light is contrary to the directed radius the sign is *negative.* The light is then passing outward from a point or the rays are *diverging;* it may be considered as negative convergence. All light encountered in Nature is of this type; converging beams of light owe their existence to lenses or curved mirrors.

It is customary to express the radius in *meters;* light diverging from a point source would thus have at 1 m. a curvature of -1; at 2 m., of $-\frac{1}{2}$; at 1 kilometer, of $-\frac{1}{1000}$; at an infinite distance, of $-\frac{1}{\infty}$, or 0. Similarly, light converging toward a point 1 m. distant has a curvature of $+1$ and toward an infinitely distant point of 0, that is, shows a plane wave front.

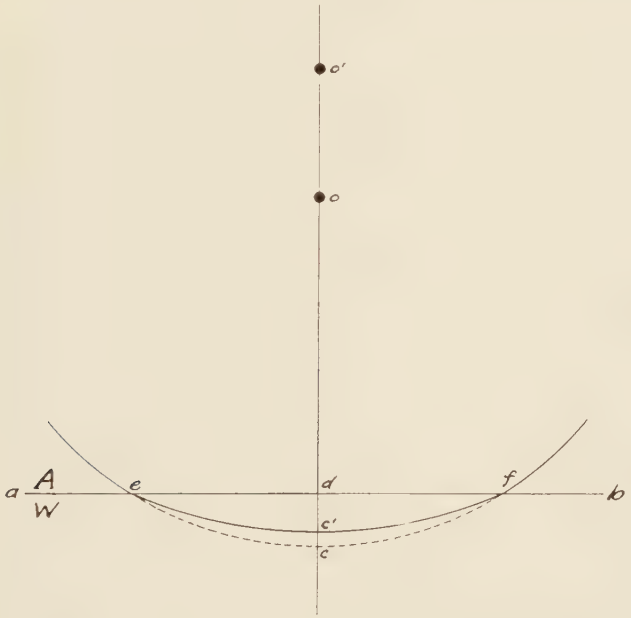

FIG. 84.—Refraction at a plane surface, wave-front method. See text.

We may now consider by this method a case similar to the first above, but with the light source at a finite distance from the air-water surface. Let *o* (Fig. 84) represent the source and *ab* the surface between air (*A*) and water (*W*). At a certain time the wave front would have occupied the position *ecf* had it not encountered the second medium. Since, however, its velocity in water is

less than in air, the front will actually be found in the position $ec'f$ determined by the relation,

$$\frac{dc}{dc'} = \frac{\text{velocity in air}}{\text{velocity in water}} = \frac{4}{3}.$$

That is, the *sagittæ*, as the segments dc and dc' of the radii r $(= oc)$ and r' $(= o'c')$ of the two wave fronts are called, are proportional to the velocities of light in the respective media and have in the present case of air and water the ratio of $\frac{4}{3}$. The sagittæ are related to the radii of the spheres and the curvatures in the following manner. Since the products of the segments of two intersecting chords are equal,

$$dc \times (2r - dc) = ed \times df.$$

and since ed and df are equal,

$$dc = \frac{ed \times df}{2r - dc} = \frac{ed^2}{2r - dc}$$

and similarly,

$$dc' = \frac{ed^2}{2r' - dc'}$$

Dividing one equation by the other we have,

$$\frac{dc}{dc'} = \frac{ed^2}{2r - dc} \times \frac{2r' - dc'}{ed^2} = \frac{2r' - dc'}{2r - dc}$$

Since dc and dc' must, in practice, form very small parts of the radii under consideration, they may be neglected without serious error and the above written:

$$\frac{dc}{dc'} = \frac{2r'}{2r} = \frac{r'}{r}$$

That is, the sagittæ are inversely proportional to the radii of the two wave fronts. Since we have shown that the curvatures of the wave fronts are inversely proportional to these radii, it follows that the sagittæ are directly proportional to the curvatures

$$\frac{\text{curvature } ecf}{\text{curvature } ec'f} = \frac{dc}{dc'}$$

The wave front in the water then proceeds as if it had originated at o' (origin and wave front both supposed to be in water) at a distance of $o'c'$, bearing to oc, an inverse proportion to the velocities in the media in which the wave fronts lie.

$$\frac{o'c'}{oc} = \frac{\text{velocity in air}}{\text{velocity in water}}$$

If, for example, the source of light is 1 m. from the air-water surface, the apparent source in water would be $1\frac{1}{3}$, or $\frac{4}{3}$ m. distant from this surface, or, expressed in curvatures, that in air will be -1, and that in water $\frac{-1}{-\frac{4}{3}} = -\frac{3}{4} = -0.75$.

With the progress of the wave front through any medium there is a gradual change of curvature with the change of radius; when, however, the wave front passes from one medium to another (except in the rare case of two media of the same refractive index) there occurs an abrupt change of curvature which may be calculated by the method indicated.

Lenses. -Space requires that many cases of refraction be omitted and that we take up a consideration of lenses which are the chief means of image formation. A *lens* may be defined as a *portion of an isotropic* (*i. e.*, optically homogeneous) *transparent substance bounded by polished faces of regular geometrical form, one of which may be a plane.* The lenses here treated must be considered as a slight curvature and of negligible thickness. Glass is the only substance commonly employed for lenses. The forms of lenses are varied; we need only consider those bounded by planes and portions of spherical surfaces. These may be divided into two types—those thicker in the center than at the edges (plano-convex, double convex and meniscus in which the convex surface is the more curved) and those thinner in the center than at the edges (plano-concave, double concave and meniscus in which the concave surface is the more curved); for the present the lenses of each type may all be considered equivalent.

It will be clear that a plane wave front in air encountering a lens will be most retarded by the thickest portion. If this is in the center the emerging wave front will be retarded in the center, that is, will have a positive curvature or consist of converging rays. A lens of this type, thicker at the center, is thus called a *convex*, a *converging*, or, since it gives to the plane wave front a positive curvature, a *positive* or "*plus*" *lens*. In contrast, a lens thick at the edges or concave will retard the light at the margins and the emerging front will have a negative curvature, or consist of diverging rays and is called a *diverging* or *negative* lens.

It is possible to trace a ray of light through a lens by considering the surface as a plane tangent to the point of incidence and constructing the angles of incidence and refraction as outlined above. For our purposes it will be advantageous, however, to pass over this method (which may be found in any standard text of physics) and to treat lenses in two other ways.

In Fig. 85 AA' passing through the centers of curvature of the surfaces of the lens is the *optic axis* and N the *nodal* point on the

optic axis midway between the surfaces. A ray having the direction AN will pass through the lens without deviation following the optic axis. A ray oblique to the optic axis through N as BB' will also suffer no deviation (in the case of an ideally thin lens). All other rays will be deviated. For example, a ray CD parallel to the optic axis AA' will, after refraction, intersect the axis at a point F_2 determined by the curvature and refractive index of the glass composing the particular lens. For a small ideally thin lens all other rays parallel to AA' will also pass through F_2, which is called the *second focal point.*

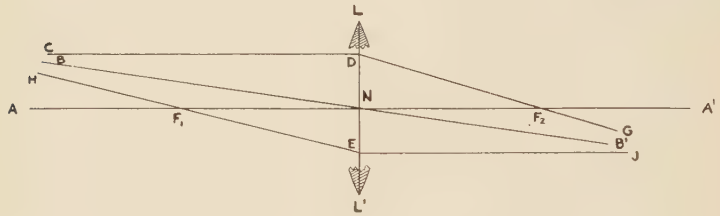

Fig. 85.—Convex lens; course of chief rays. See text.

Similarly, rays passing through a point F_1, the *first focal point* (in this case as far to the left of N as F_2 is to the right) will, after refraction, take a course parallel to the optic axis. Thus a point source infinitely distant to the left and giving a plane wave front or parallel rays will have an image at F_2, and a point source at F_1 will give off rays that, after refraction, will be parallel or the wave front will be plane.

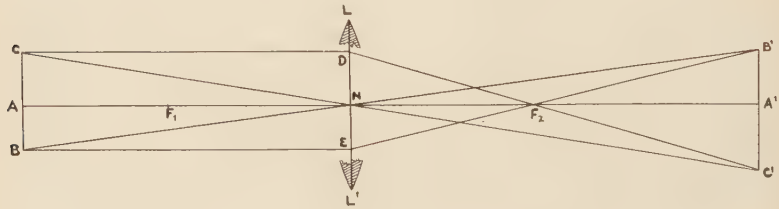

Fig. 86.—Convex lens; formation of image. See text.

Experimentally, the distance NF_2 (or NF_1, which for a small thin lens will be the same) may be determined, and from this, even though the curvature of the lens surfaces and its index of refraction are unknown, rays may be traced and images constructed. Thus, in Fig. 86, where LL' represents a lens with the optical axis AA', and first and second focal points F_1 and F_2, let CB represent the two extremities of an object. A ray from C parallel to the optic

axis (CD) will, after refraction, pass through F_2 and intersect ray CN passing through the nodal point N at C'. C and C' are *conjugate points* (or *foci*); all light from C that falls upon the lens is reunited at C'. Similarly B and B' are conjugate points. It may be shown that for each point of the object CB a conjugate point exists in $C'B'$, which is therefore the image of CB.

This method is a general one and if it is remembered that under certain conditions the rays may not intersect in a *real image*, but that their prolongations may intersect in a *virtual image* from which the rays appear to diverge, it may be applied to all cases of converging or diverging lenses.

Between the many possible pairs of conjugate points of which, it may be pointed out, the first and second focal points represent a special case, since each is conjugate to an infinitely distant point on the optic axis, there exists a relation extremely useful in treating images. This we will develop briefly. In Fig. 86 triangles NF_2E and $A'F_2B'$ are similar, since they have right angles at N and A' and equal angles at F_2.

Therefore:

$$\frac{NE}{A'B'} = \frac{NF_2}{F_2A'} \tag{1}$$

and since $NE = AB$ we may substitute, giving

$$\frac{AB}{A'B'} = \frac{NF_2}{F_2A'} \tag{2}$$

Also triangles ABN and $A'B'N$ are similar and hence as above

$$\frac{AB}{A'B'} = \frac{NA}{NA'} \tag{3}$$

Therefore:

$$\frac{NF_2}{F_2A'} = \frac{NA}{NA'} \tag{4}$$

We may now substitute in this equation (4) symbols for the chief distances, with the following convention regarding signs. As stated, light is supposed to pass from left to right. All distances are measured from the lens (nodal point); distances measured in the direction of propagation of the light are positive; distances against the light negative. Obviously, if the direction of light is reversed the proper change of signs leaves all relations the same:

$NF^2 = f$ = focal length.
$NA = -o$ = object distance.
$NA' = i$ = image distance.
$F_2A' = NA' - NF_2 = i - f.$

We obtain

$$\frac{f}{i-f} = \frac{-o}{i} \tag{5}$$

$$if = -io + fo \tag{6}$$

Dividing by *iof* we obtain

$$\frac{1}{o} = \frac{-1}{f} + \frac{1}{i} \tag{7}$$

or

$$\frac{1}{f} = \frac{1}{i} - \frac{1}{o} \tag{8}$$

This is the familiar formula stating that the sum of the reciprocals of the object distance and of the image distance equals the reciprocal of the focal length. This is also a general formula and may be applied to all cases if the above convention of signs and of distances is observed. Real images have positive distances; virtual images, negative distances.

The action of lenses may also be treated by following the changes in curvature of the wave front, a method which though less familiar is extremely useful in ophthalmology. A lens impresses on a wave front a new curvature, a converging or positive lens giving to a plane wave front (curvature 0) a positive curvature (convergence), to a positive wave front a greater positive value and to a negative wave front a less negative or a positive value, according to the refractive power of the lens. A plane wave front after passing through a positive lens will converge toward the second focal point; its curvature will therefore equal the reciprocal of the focal length, or $\frac{1}{f}$. This fact has been made the basis of lens notation. The unit curvature is one with a radius of 1 m.; this is called the *diopter* (also written *dioptry* and abbreviated as D or *dptr.*). A converging lens giving to a plane wave front a curvature of +1 is said to have a refractive power of 1 D. *The refractive power of a lens is equal to the reciprocal of the focal length in meters.*

Let us now consider the effect of a lens of +5 D placed in the path of light. If the entering wave front is plane it will emerge with a curvature of +5 D and converge to a focal point $\frac{1}{5}$ m., or 20 cm. beyond the lens. If the entering wave front has a curvature of +3 D this will be increased to +8 D (+ 3 + 5), thus coming to a focus at $\frac{1}{8}$ m., or 12.5 cm. If the wave front is diverging, for example −2 D, it will be altered to +3 D (− 2 + 5), or if it is −7 it will become −2 (7 + 5), that is, the front will become positive or less negative, depending upon the relative degree of curvature of the wave front and the refractive power of the lens.

It will be noted that the terms in the equation

$$\frac{1}{f} = \frac{1}{i} - \frac{1}{o}$$

since they are reciprocals of distances may conveniently be taken as curvatures and treated as in the above example. Expressed in words, the equation thus becomes: *The algebraic sum of the curvatures in diopters of a wave front entering a lens and the refractive power of the lens (the curvature that the lens will impress on a plane wave front) is equal to the curvature of the emerging wave front.*

Two or more thin lenses of low refractive power placed in contact will affect wave fronts as would one lens having a refractive power equal to their algebraic sum. This is a fact of practical importance in dealing with ophthalmic lenses which usually fulfill the above conditions with sufficient accuracy to make the results reliable.

IMAGE FORMATION IN THE HUMAN EYE.

We are now in a position to take up the image-forming apparatus of the eye. This includes, as we have said, the media which an entering ray of light will encounter and the light-excluding structures. Light will pass successively through a layer of *tears*, the *cornea*, the *aqueous humor*, the *lens*, the *vitreous body* and part of the *retina*.

Tears.—Although the tears are not usually considered as having any optical significance and cannot be called a refracting medium they nevertheless furnish the refractive surface separating the eye from the air, a situation unique in optical instruments. When winking is voluntarily suspended, part of the dimming of vision that everyone has noticed is due to the gradual impairment of this surface by drying.

Cornea.—The cornea presents an almost complete transparency due, as previously stated, to the homogeneity of its physically diverse structures; this transparency is impaired by chemical changes in the body fluid or undue tension. The shape of the cornea is important since at its surface the chief refraction of the eye takes place. It is, according to Collins, relatively smaller in man than in most mammals, being less than one-half the diameter of the bulb, whereas it is more than one-half in the cat or horse. This acts to reduce man's field of view but increases the refracting power of the cornea. Its central portion has a radius of approximately 7.8 mm. (80 per cent of all eyes lie between 7.5 and 8.1 mm.); the peripheral parts are less curved. It is not normally symmetrical, but following, as has been pointed out, the shape of the bulb is more curved in the vertical than in the horizontal meridian (p. 583). Its index of refraction is a little greater than that of water, equalling 1.376.

The aqueous humor and the vitreous body have a refractive index practically identical with that of water (1.336) and no form of their own, their surfaces being determined by the structures confining them. Normally they are as transparent as water.

Lens.—The crystalline lens is an optically complex body of especial interest. Like the cornea, its structural elements show no sharp changes of optical density, although there is a gradual increase of refractive index from the surface inward, paralleling the increasing physical density that we have noted. The successive layers, moreover, do not have the same shape but become more convex in passing inward. Furthermore, both its shape and its consistency (and presumably its optical density) change with age. In fetal life it is nearly spherical, but becomes less convex with age, until in a young adult the unaccommodated lens has a radius of curvature of approximately 10 mm. for the anterior surface and 6 mm. for the posterior surface. In accommodation, as we shall see, these curvatures become greater -about 6 mm. for the anterior and 5.5 mm. for the posterior.

Owing to the unique fact, not paralleled by man-made optical instruments, that the optical density varies from part to part becoming greater from the surface toward the center, the refractive effect of the lens is difficult to investigate or to state in simple terms. The refractive power of the crystalline lens is greater than that of a simple homogeneous lens, having the same curvatures and an index of refraction equal to the average found for the different parts or even to the maximum found for the crystalline lens. This is due in part to the fact that the greater central density as compared with the periphery would retard the light here and produce converging rays, even were the faces plane and parallel. The actual determinations of the refractive index vary from about 1.382 for the outer layers to 1.406 for the center.

In general, corresponding to the fact that the cornea of man has greater refractive power than in most mammals, the lens has less bulk and less refractive power, a fact making possible man's greater power of accommodation.

The remaining medium traversed by light is the retina through the greater thickness of which the light must pass before the true receptors are reached. Though apparently different in density from the vitreous, its effect on the course of light is negligible.

Light Exclusion.—The opacity of the sclera and the pigment of the chorioid, retina and iris combined to exclue, under ordinary circumstances, all light except that entering through the pupil. The importance of this light exclusion is shown by the plight of albinos in whom the pigment is lacking. As a result, the scattered light entering through the iris and sclera renders vision poor and

bright light very unpleasant. Another feature affecting the optical state of the eye is the constancy of the interocular pressure (page 588).

Schematic Eye.—The refraction in the eye occurs at four surfaces—the anterior and the posterior surface of the cornea, the anterior and the posterior surface of the lens. The optical system thus presented is complicated and the data used for calculating retinal images or similar purposes is usually simplified in some degree. For example, the anterior and the posterior surfaces of the cornea are nearly parallel and the density or refractive index of the cornea but little greater than that of the aqueous; it is thus possible to assume that refraction occurs only at the anterior surface of the cornea without appreciable error. The refractive power of the cornea calculated on this basis is about 43 D and that of the lens 20 D, or less than one-half as much—a fact not surprising when we consider that the greatest difference of refractive index occurs between the air and the cornea and not between the lens and the aqueous humor or the vitreous body. In man the lens is less refractive and the cornea more refractive than in most mammals—a fact of significance in connection with accommodation.

The following are some of the more useful data for the "schematic" eye, which represents simplified average values for a young adult man.

VALUES FOR SIMPLIFIED SCHEMATIC EYE. (GULLSTRAND).

Index of refraction of aqueous and vitreous	1.336	
Index of refraction of (equivalent infinitely thin) lens	1.413	
Radius surface of (equivalent) cornea	7.8	mm.
Radius of anterior surface of lens	10.0	"
Radius of posterior surface of lens	−6.0	"[1]
Optical center of lens from anterior surface of cornea	5.85	"
First principal point from anterior surface of cornea	1.505	"
Second principal point from anterior surface of cornea	1.631	"
First focal point from anterior surface of cornea	−15.235	"[1]
Second focal point from anterior surface of cornea (also position of fovea)	23.996	"
Refracting power of cornea	43.08	D
Refracting power of lens	20.53	D
Refracting power of complete system of eye	59.74	D

[1] Negative values represent distances measured backward along the course of light entering the eye or points in front of the cornea. (See Helmholtz's Physiological Optics, English translation, vol. 1, p. 354.)

Reduced Eye.—Even this schematic eye necessitates calculations which are sometimes involved; for many purposes the still simpler *reduced eye* is sufficiently accurate. In this (Donders) the refraction occurs solely at one ("corneal") surface between air and a single medium with the refractive index of water ($\frac{4}{3}$), which is little below that of the aqueous humor and vitreous body.

Reduced Eye.

Index of refraction	1.33
Radius of cornea	5.0 mm.
Optical center (nodal point and center of curvature) from anterior surface of cornea	5.0 "
First and second principal points from anterior surface of cornea	0.0 "
First focal point from anterior surface of cornea	−15.0 "
Second focal point from anterior surface of cornea (also position of fovea)	20.0 "
Refracting power of eye	66.67 D

A diagram of this reduced eye, actual size, is given in Fig. 90A. If, for example, we wish to calculate the size of the retinal image at any considerable distance from the eye it may readily be done from these data. The undeflected rays from the extremities of the object to the extremities of the image will form two similar triangles, $N\,C\,B$ and $N\,C'\,B'$. (See Fig. 86.)
Therefore

$$\frac{CB}{NA} = \frac{C'B'}{NA'}$$

or

$$\frac{\text{length of object}}{\text{distance of object}} = \frac{\text{length of image}}{\text{distance of image from nodal point}}$$

If, for example, the object is a window 1.2 m. in height in a house 100 m. distant, the size of the retinal image will be given by the equation

$$\frac{1.2}{100} = \frac{x}{0.015} \qquad x = 0.00018 \text{ m., or } 0.18 \text{ mm.}$$

Visual Acuity.—Visual acuity, the measure of the power of the eye to perceive form or, more specifically, to distinguish as separate adjacent objects, depends not only on the optical condition of the eye but also on the condition of the retina. Since, however, visual acuity is universally used as a criterion in determining the refractive state of the eye, the topic may be introduced here. An object seen by the eye subtends an angle dependent upon its size and distance; this is called the *visual angle*. For distant objects it is of little consequence at what point the angle is measured; for near objects with the data of the reduced eye the nodal point is used, although more accurate calculations can be made using the first principal point of the schematic eye. In order that two objects, such as stars or parallel lines, may be distinguished they must be separated by a minimum visual angle. This angle varies with the individual; a value of 1′ (or 2′ from center to center of two adjacent lines) has been accepted as normal for the human eye, and on this

basis are constructed the test types introduced by Snellen in 1862. Fig. 87 shows an *E* of the form commonly used; it will be seen that all bars and spaces are equal, having a width which at the proper distance, in this case 6 m., subtends 1′, so that the entire letter is 5′ in height. If such a letter can be read, the visual acuity is considered 1; if larger or smaller type must be used the visual acuity is taken as the reciprocal of the necessary visual angle; thus, if the strokes of the letter must be 2′ wide to be read the visual acuity is $\frac{1}{2}$. In practice it is usual to express the result of such an examination as a fraction in which the denominator represents the distance for which the type was designed and the numerator the distance at which it can be read. Thus if the test is made at 6 m., and only that type intended to be used at 12 m. can be read, the result will be recorded as $\frac{\text{VI}}{\text{XII}}$. The relation of this test to retinal function will be discussed later (page 662).

Fig. 87.—A letter used in testing visual acuity, showing method of construction. When viewed from 6 meters each block subtends an angle of 1′.

Optical Defects Influencing Image Formation.—The main features of image formation in the eye have been outlined. Any type of optical defect or aberration affecting the formation of images by lenses may also affect the working of the eye. As in the case of optical instruments, the size of the "stop" or diaphragm, represented in the eye by the pupil, is an important factor in image formation. In addition, the retina under particular conditions has a threshold for each wave length of visible radiation, so that all portions of the physical image falling below this intensity are ineffective, and there exists a *physiological image* which may, from the exclusion of the extremely deviated light, be more satisfactory than the physical. Thus, the image of a star or of a fine line is flanked by light and dark diffraction bands, which, however, are only exceptionally bright enough to stimulate the retina and reduce the sharpness of the boundaries of the image.

So-called *spherical*, or *monochromatic aberration*, is present in the eye as in other optical instruments having approximately spherical surfaces. For several reasons, however, its effect is not serious; the shape of the cornea, which, as we have said, is not spherical, the structure of the lens and the elimination of the extreme peripheral zones of both by the iris all lessen its effect. Only a small portion of the image near the optic axis is used in distinct vision, and hence the distortion of the peripheral part of the image is of little

consequence. One form of monochromatic aberration of more importance, that resulting from lack of sphericity in the refracting surfaces, will be considered later under astigmatism.

More serious are those defects resulting from lack of harmony between the refractive power of the various surfaces and their distance from the retina. If the focal point of the entire system of the eye does not fall upon the retina clear images will, of course, be impossible. The degree to which the image is defective will depend upon two factors—the distance of the focal point from the retina and the size of the pupil. The convergent bundle of rays within the eye will form a cone with the pupil as a base and the focal point as the apex, beyond which if not intercepted the light expands into a second cone of the same angle. If intercepted by the retina at any place other than the focal point, the section of the cone will form a circle with a diameter dependent upon the distance from the apex and the slope of the cone which is determined by the size of its base, the pupil. The size of these *blur* or *diffusion circles* is a measure of the clearness of the image The improvement effected by the narrowing of the pupil is very marked, but it should not rashly be concluded that the smallest pupil is the best. Aside from the reduction of the amount of light, the small pupil gives rise to *diffraction* effects, which impair the image. Because it affects the size of the blur circles the size of the pupil influences the *depth of focus* or range in distance of objects that are satisfactorily in focus; this is greater the smaller the pupil.

The *focal defects*, as they may be called are an important feature of the eye and have received much attention from the ophthalmologist, since it is these that impair vision and require spectacles. Before they can be considered profitably, however, it is necessary to take up accommodation.

Accommodation.—So far we have been treating the eye as a static instrument with surfaces of fixed refractive power and set at fixed distances from the retina. For any optical instrument a series of image points conjugate to a series of object points lying at different distances will themselves lie at different distances from the refracting surface. Clear images of all objects, therefore, cannot be formed on one screen at one time and the instrument must be focussed or adjusted for different objects. That the eye formed no exception to this rule was realized by a number of early workers, but it remained for Thomas Young, in 1801, clearly to formulate and examine the problem of *accommodation* or adjustment of focus of the eye.

Of the various hypotheses in the field, three only he considered theoretically possible: (*a*) That changes occur in the curvature of the cornea; (*b*) that changes occur in the curvature of the lens; (*c*) that changes occur in the length of the eye. By ingenious experi-

ments he proved that neither the curvature of the cornea nor the length of the eye was altered during accommodation. He found that eyes in which the lens had been removed for cataract had no power of accommodation and, therefore, concluded that the changes occur in the lens. These observations are as satisfactory today as when made. It was not until half a century later that Langenbeck and Cramer independently observed the changes taking place in the images reflected from the lens and gave easily verified proof that Young's view is correct. If a candle is held before and a little to one side of an eye, which is then observed from the opposite side, three images may be seen reflected in it. The brightest, erect and small, comes from the anterior surface of the cornea (with care a second very close to the first but much fainter can be made out from the posterior surface of the cornea), a larger erect and less distinct image comes from the anterior surface of the lens, while the third small inverted image comes from the posterior surface of the lens. If now the person accommodates without changing the direction of regard no change will be seen in the first or corneal image, the second (from the anterior surface of the lens) will be seen to become smaller and more distinct, while the third will alter so little that the change may not be detected.

Helmholtz was the first to offer a satisfactory explanation of the mechanism by which the shape of the lens is altered. Work since his time has served to strengthen his view. It should be noted, however, that his explanation applies only to man and other mammals; accommodation in other vertebrates is known to differ in many essential features.

The anatomical situation is briefly as follows (page 586). The lens at the ages during which extensive accommodation is possible consists of a semifluid or jelly-like body enclosed in an elastic capsule. The capsule is attached by the numerous fibers of the suspensory ligament (zonule of Zinn) to the ciliary processes. The eye at rest is accommodated for distant objects and its surfaces are then the least curved. If, however, the lens of a fresh eye is freed from its attachment by cutting the suspensory ligament it becomes more convex, showing that its flattened shape was the result of tension upon its equator.

Within the ciliary body lies the ciliary muscle, consisting, as pointed out, of radial and circular fibers (Fig. 88). The radial fibers have their origin in the sclerotic near the base of the iris, as may be noticed in a fresh eye when the retina and chorioid are stripped from the sclerotic. The opposite ends of the radial fibers are inserted diffusely into the chorioid. The contraction of the radial fibers will, therefore, result in drawing the elastic and loosely attached chorioid forward and inward toward the base of the iris, with a corresponding relaxation of the suspensory ligament. The

circular fibers in contracting would form a smaller ring and thus supplement the action of the radial fibers. When the tension of the suspensory ligament is relaxed the elasticity of the capsule increases the convexity of the lens. The change is greatest in the anterior surface in which during vigorous accommodation on a

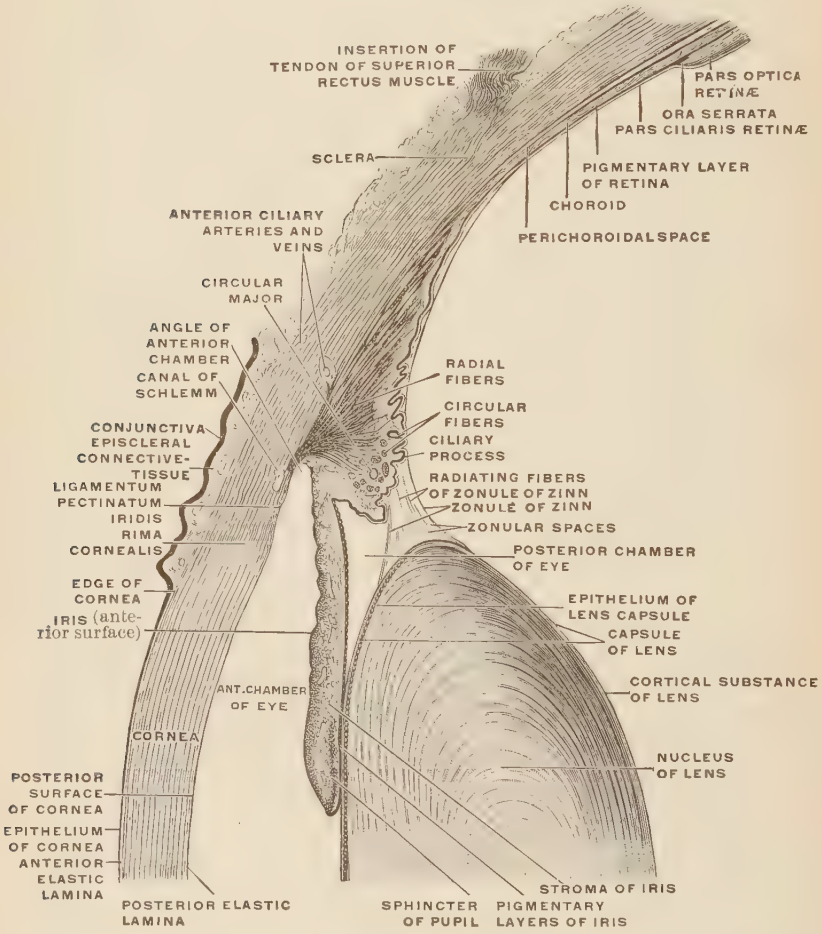

FIG. 88.—The upper half of a sagittal section through the front of the eyeball. (Gray's Anatomy.)

point 10 cm. in front of the cornea the radius decreases from 10 mm. to 5.33 mm., while the posterior surface changes from 6 mm. to 5.33 mm. The greater change in the anterior surface has been ascribed to the fact that the anterior portion of the capsule is thicker than the posterior.

Opposing views of the mechanism of accommodation have been advanced, but all careful work since the time of Helmholtz has served to support his view. It is sufficient to cite the experiments of Hess, showing that during strong accommodation the lens sinks slightly under the influence of gravity toward whatever part of the eye is lowest at the time, a condition that can only mean that all tension on the suspensory ligament is at this time relaxed.

The power of accommodation is shown by the variation in distance of objects that may be focussed by the eye. The point that is imaged accurately on the retina without accommodation is called the *far point;* the nearest for which the eye can be accommodated, the *near point.* The far point is the point conjugate to the retina of the unaccommodated eye; the near point, that conjugate to the retina of the accommodated eye. For the average eye the far point is at infinity and the near point at a distance of a few centimeters. Since the near point varies with age, no average figure can be given; let us assume that for a particular case it is 12.5 cm. For such a person there would be a *region of accommodation* extending from 12.5 cm. to infinity within which objects could be seen distinctly. This, however, is not a convenient measure of accommodation, as the same change in the eye will be comprised within a few centimeters if the two points are near the eye or spread over immense distances if the far point is at infinity. The *amplitude* of accommodation is better measured in diopters. If the far point is infinity the wave front meeting the eye has a curvature of $\frac{1}{\infty}$ or 0 D. The near point of the above example will, on the other hand, give rise to a wave front with a curvature of $\frac{-1}{0.125}$, or -8 D. The refractive power of the eye has obviously been altered 8 D by accommodation. We may define the *amplitude of accommodation* as the *degree of alteration in the refractive power* of the eye and measure it in diopters according to the relation:

$$A = C_{fp} - C_{np}$$

where A = amplitude of accommodation
C_{fp} = curvature of wave front from far point
C_{np} = curvature of wave front from near point
or the equivalent expression,

$$A = \frac{1}{fp} - \frac{1}{np}$$

where fp and np are the far and near point distances in meters. It will be noted that real far and near point distances measured in accordance with the conventions for other lenses (page 601) are

both negative. That is, the increased convergence produced by accommodation may be duplicated by a convex or positive lens of the refracting power given by the above formula placed before unaccommodated eye (strictly speaking at the first principal point). Thus in the above example

$$A = \frac{1}{\infty} - \left(-\frac{1}{0.125}\right) = 0 + 8 = 8\,\mathrm{D}$$

The limiting factor for amplitude appears to be the physical state of the lens which determines the degree of convexity that

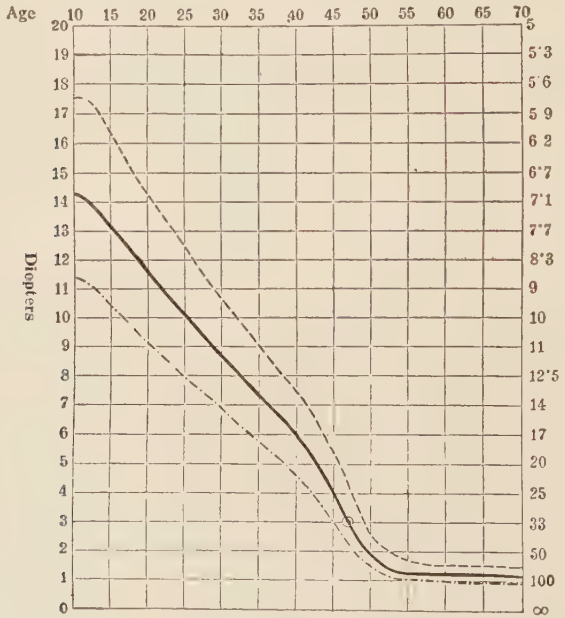

Fig. 89.—Amplitude of accommodation at various ages. (Duane.) Age is given at the top of the figure. At the left is given the amplitude in diopters (as measured by a lens placed at the first principal focus of the eye, 13 mm. in front of the cornea). The figures on the right are the focal lengths of such lenses. The solid line is the average observed, the dotted lines the maximum and minimum for the ages. The circle on the average at 3 D is the conventional limit of presbyopia. (de Schweinitz, "Diseases of the Eye," W. B. Saunders Co., Publishers.)

will be assumed when all tension is removed from the suspensory ligament. As stated, the firmness of the lens increases with age and, in consequence, the amplitude of acccommodation steadily decreases from 13 or 14 D at ten years of age to 1 D or less in old age, as shown in Fig. 89. Certain consequences of this reduction of accommodation will be considered later.

The amplitude of accommodation in man is greater than in other mammals, although probably less than in many birds. This, as before suggested, is associated with the greater convexity of the cornea and the lesser convexity of the lens in man. In consequence, possible changes in the shape of the lens produce greater alteration of the refractive power than in the already nearly spherical lenses of most mammals.

FOCAL DEFECTS.

Having treated accommodation it is now possible to consider the focal defects mentioned above (page 607).

Emmetropia.—Emmetropia is that condition in which the *second focal point of the unaccommodated eye falls in the sensitive layer of the retina* or in which the *far point is infinitely distant.* By such an eye, therefore, distant objects may be seen without effort. The near point, as stated, varies with age and is not a factor in defining emmetropia. It should also be noted that emmetropia results from a proper relation between the refractive power of the cornea and lens and their distance from the retina and not from fixed values for any of these factors.

Ametropia.—Ametropia is any deviation from this optically ideal relation and comprises myopia and hyperopia, as well as astigmia. Although myopia and hyperopia may result from either abnormal axial length or abnormal curvature, the former is by far the more common, and in discussing these defects it will be assumed that they are due to disproportionate axial lengths.

Myopia.—Myopia is that condition in which the *second focal point of the unaccommodated eye falls in front of the sensitive layer of the retina* or in which the *far point lies at some finite distance from the eye* (in practice a distance of less than the 6 m., or 20 feet, at which examinations are made). Usually this results from too great an axial length and, in consequence, the focal point lies in the vitreous while the retina is reached by a diverging cone of light forming a *blur circle.* Because of the greater axial length the *near point* lies nearer to the eye than in an emmetrope of equal amplitude of accommodation.

Hyperopia.—Hyperopia (or hypermetropia) is that condition in which the *second focal point of the unaccommodated eye lies behind the sensitive layer of the retina.* There is, therefore, *no real far point* or point conjugate to the retina of the unaccommodated eye. The *far point is virtual* and represents the point of intersection of those rays having the degree of convergence necessary to focus upon the retina; its position is behind the eye. By increasing the refracting power of the eye through accommodation distant objects may be focussed on the retina, so that, unlike the myope, the hyperope

can see distant objects but at the expense of accommodative effort. The *near point* of the hyperope is more distant than that of the emmetrope of equal amplitude of accommodation, since part of the accommodation is expended in converging parallel rays, so that they may focus on the retina and less is left to converge the light from still nearer objects.

Because both the far and near points of the myopic eye are nearer than those of the hyperopic eye, myopia is commonly called short-sightedness or near-sightedness and hyperopia far-sightedness; unfortunate terms since they have misleading implications. Thus, it is often inferred that a "far-sighted" person can see "farther" or at least better in the distance than can a person with normal vision, whereas the emmetrope sees equally well in the distance and without the accommodative strain of the "far-sighted" person.

Since we have definied emmetropia as the condition in which the retina is conjugate to infinity, the degree of focal defect or ametropia may be measured by the reciprocal of the far point of the eye, or, to express in other words, the curvature of the wave front, which may be utilized by the eye at rest. It should be noted that this expression will have a value of 0 for emmetropia; any finite value indicates a focal defect and its sign the type. Thus, if the far point is at 2 m. the far point wave front has a curvature of $-\frac{1}{2}$ D and the eye is myopic $\frac{1}{2}$ D; whereas if the far point is 25 cm. behind the eye, the curvature is 4 D and the eye is 4 D hyperopic. It will be noted, and this is an important fact, that if a lens of the sign and power of the far point curvature is placed before the eye at rest parallel rays will be focussed on the retina. Thus a -0.5 D lens will give to parallel rays a divergence equal to that of rays from an object 2 m. distant, or a $+4$ D lens will give to parallel rays a convergence equal to those advancing toward a point 25 cm. distant.

In Fig. 90 are given diagrams of emmetropia and the two types of focal defects. *A*, *B* and *D* show the path of parallel rays in emmetropia, myopia and hyperopia respectively; since the defects are axial the rays in each case come to a focus at the same distance from the cornea. The upper half of *C* shows the course of light from the far point; the lower half, the effect of an appropriate concave lens which gives to the light entering the eye the same course as it would have had if it had come from the far point; *E* is a similar treatment of hyperopia. Rays converging toward the virtual far point of the hyperopic eye, as shown in the upper half are, of course, not actually encountered in Nature. Since the path of light is reversible, *A*, *C* and *E* may also represent the course of light from the retina, as in the use of the ophthalmoscope. The main point is that the wave front between the correcting lens and the eye has the curvature of light from the far point of the uncorrected eye.

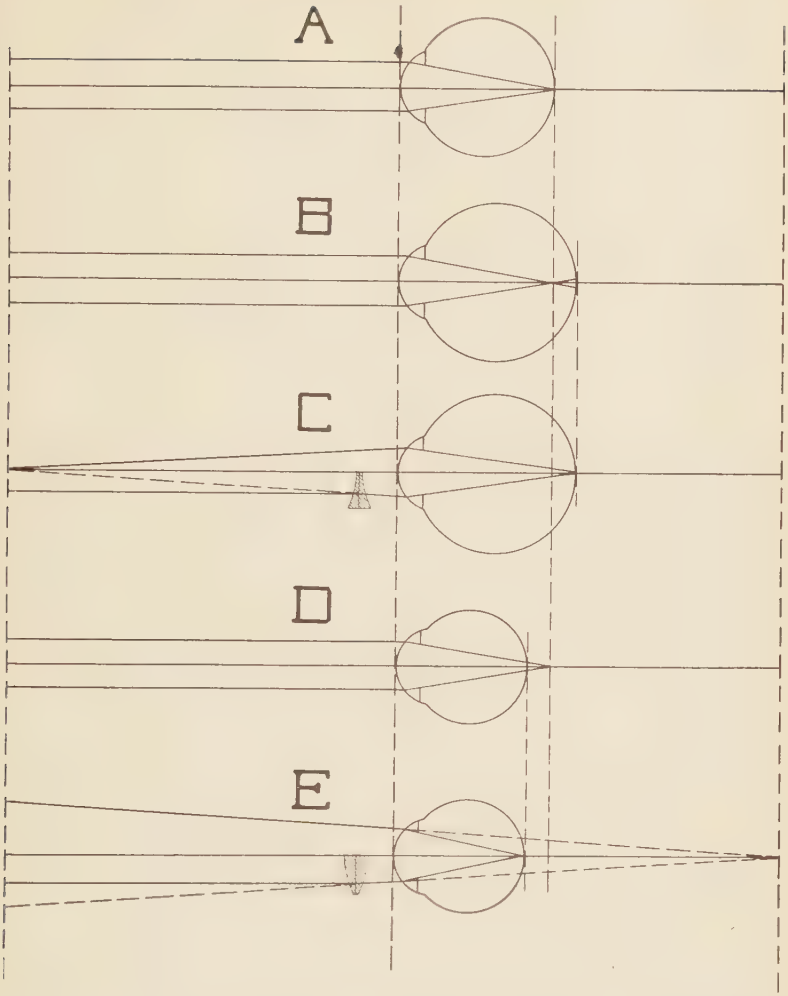

FIG. 90.—Emmetropia and the two focal defects, myopia and hyperopia, with their correction. *A* represents the course of parallel rays in an emmetropic eye (reduced eye, actual size). *B* uncorrected myopia with the second focal point at same distance from cornea as in *A*. (The actual shape of myopic, or hyperopic eye not represented, except as regards axial length.) *C*, upper half, light from far point of myopic eye focussing on retina; lower half, with correcting concave lens showing that light reaching the cornea has the same course as that from the far point, as shown by the dotted line. *D*, uncorrected hyperopic eye; *E*, upper half, light converging toward virtual far point (indicated by dotted lines) focussing on retina; lower half, with correcting convex lens showing that light reaching cornea has same course as that toward far point. Of course converging rays as in upper half of *E* not encountered in nature. *A*, *C*, and *E* may also represent course of light from an illuminated retina as in the use of ophthalmoscope.

The following table gives the near and far points for emmetropia and various degrees of ametropia in eyes having the same amplitude of accommodation.

	Degree of defect. D.	Far point distance. M.	Near point distance. M.	Far point curvature, 1/fp. D.	Near point curvature, 1/np. D.	Amplitude of accommodation. D.
Emmetropia . . .	0	∞	0.125	0	− 8.0	8
Myopia	0.5	2.0	0.118	0.5	− 8.5	8
	1.0	1.0	0.111	−1.0	− 9.0	8
	2.0	0.5	0.100	−2.0	−10.0	8
	5.0	0.2	0.077	−5.0	−13.0	8
Hyperopia . . .	0.5	−2.0	0.133	0.5	− 7.5	8
	1.0	−1.0	0.143	1.0	− 7.0	8
	2.0	−0.5	0.166	2.0	− 6.0	8
	5.0	−0.2	0.333	5.0	− 3.0	8

This table illustrates how from the formula relating far point, near point and amplitude (page 611) any of these quantities may be obtained if the other two are given. It also shows that the region of accommodation decreases with increasing ametropia if eyes of equal accommodative activity, as measured by the amplitude, are compared.

Although a text-book of ophthalmology should be consulted for details concerning these defects, some facts of physiological interest may be cited here. Hyperopia is nearly universal among infants and very common in children and may be looked on in part as a stage of incomplete growth. It is also said to be common among wild mammals.

Emmetropia becomes more common with growth approximately up to puberty. Myopia is rare among children and has been found more common with increasing age. High degrees of myopia are often associated with structural changes in the eye and may then be looked upon as pathological. Although there exist difference of opinion as to the cause of these defects there is general agreement that their correction by proper spectacles not only prevents much discomfort and permits activities otherwise impossible, but has a favorable effect on such pathological changes as tend to be progressive.

Astigmatism.—Another defect not coördinate with myopia or hyperopia is *astigmatism* (astigmia). Although meaning the absence of a point image and, therefore, strictly applicable to various defects already mentioned, it is in practice restricted to a particular form of refraction, the so-called "regular" astigmatism associated with marked differences in the curvature of various meridians of the cornea or other refracting surfaces. "Irregular" astigmatism

to which the stars owe their rayed appearance is a defect present in some degree in nearly all eyes. It should not be confused with the unrelated "regular" astigmatism which alone will be treated here.

Astigmatic refraction is complex and many features are controversial; its treatment here will have to be simplified.

It may be best studied in two forms of lens commonly used in spectacles—the cylinder and the tore. The cylindrical lens is bounded by one plane face; the other is cylindrical, either convex or concave. The toric lens has a surface generated by the revolution of a circle about an axis in its plane, but not passing through its center; such a surface is found on an automobile tire, a "slab" from which would have the form of a convex tore. In both lenses the curvatures in different meridians through the "optic axis" (if that term can be extended to apply to a line perpendicular to the plane surface through the center of the cylinder or the bearing of the automobile wheel) are unequal. It will readily be seen that such lenses could not be expected to furnish point images. The actual course of light is less readily visualized. In the case of a convex spherical lens the parallel rays after emerging converge to a point and beyond this diverge again, giving a beam with the shape of two cones apex to apex. Corresponding to this, a cylindrical lens with its axis vertical would give a beam which may be represented by two wedges placed apex to apex. In the vertical each section of the lens is uncurved and the parallel rays will be undeflected; each horizontal section is convex and emerging rays will be bent toward the axis of the lens intersecting in the "focal line" beyond which they again diverge. A toric lens or a cylindrical lens combined with a spherical give rise to a more complicated beam which may conveniently, if incompletely, be represented by the conoid of Sturm (Fig. 91). Here the vertical meridan *CD* has the greater curvature, corresponding to a focal length *AG* and the horizontal meridian *EF* a lesser curvature corresponding to *AB*. The emergent beam at first round in cross-section soon becomes an ellipse with the longer axis horizontal and finally converges to the focal line *aa'*. Beyond this the rays *CGM* and *DGL* diverge while *ENB* and *FOB* are still converging, giving first a horizontal ellipse, a circle, a vertical ellipse and a focal line *bc*, but never, it will be noted, a point.

Although this condition was recognized in the eye by Young, in 1801, it was not until 1862 that Donders made the first practical application of lenses to its correction. As we have stated (page 603), the vertical meridian of the cornea is usually more curved than the horizontal; this relation may occur between any two meridians at right angles, giving a form to the cornea closely approaching that of a tore. It produces, if present in any considerable degree, a very troublesome form of defect, not only pre-

venting clear image but giving undue emphasis to certain elements of the image, tilting lines from their apparent position and, perhaps from the constant attempts to better by accommodation an unsatisfactory image, giving rise to great eye strain.

It is beyond the scope of this book to give the various forms of astigmatism and their treatment, but two features may be mentioned. The test usually used by ophthalmologists is a chart consisting of radiating lines, which to the astigmatic eye appear of unequal brightness. It will be clear that if the retina of the eye occupies the position of the first focal line *aa'* in Fig. 91 that each

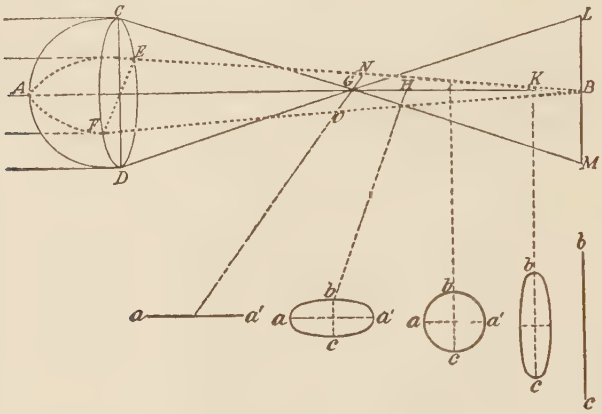

Fig. 91.—Astigmatism. Course of light through an astigmatic lens (conoid of Sturm). (McKendrick.) The cross-sections of the refracted light at various points are shown below. (Howell's Physiology, W. B. Saunders Co., Publishers.)

point of the chart will be represented by a short horizontal image. In the case of a horizontal line these will overlap, giving a sharp image, except at the ends, where a gray fringe will be seen, but that vertical lines thus imaged will be deformed into a broad gray band and be seen much less clearly.

It is plain from what we have said of the shape of the cornea responsible for astigmatism that the most refractive meridian might be emmetropic while the least curved was hyperopic, or both might be ametropic in various combinations. If to each meridian can be applied the appropriate correcting lens, which is possible by the use of a single cylindrical or toric lens, the difference of refraction can be equalized and both meridians made emmetropic.

Presbyopia.—Irrespective of the refractive state of the eye in youth whether emmetropic, myopic or hyperopic or astigmatic—its amplitude of accommodation will decline with age. When the amplitude available does not allow a comfortable reading at the customary distance of about $\frac{1}{3}$ m., that is when the amplitude falls

below about 3 D, which, as can be seen from Fig. 89, occurs between forty and fifty years of age; the eye is said to be *presbyopic*, and a supplementary convex lens is necessary for reading. The distant near point of the presbyope due to reduced accommodation should not be confused with the distant near point of the hyperope associated with a normal accommodation but resulting from an abnormal far point.

IRIS.

The iris represents an important feature of the optical system of the eye and because of this and because of its unexpectedly intricate nervous control, which makes its reactions significant in diagnosis, it has been much studied. The general features of its structure have been given (page 585). It remains to point out the nervous connections of the iris. Its two antagonistic smooth muscles, *sphincter* and *dilator*, are innervated from opposed sections of the autonomic nervous system, the sphincter from the cranial and the dilator from the thoraco-lumbar section (page 129). The preganglionic fibers to the sphincter arise in the nucleus of the third (oculomotor) nerve and pass with the third to the ciliary ganglion; from this the postganglionic fibers pass through the short ciliary nerves to the bulb, where they supply not only the sphincter but also the ciliary muscle and the local bloodvessels. The preganglionic fibers to the dilator leave the cord with the eighth cervical and the first and second thoracic nerves and pass to the superior cervical ganglion. From this the postganglionic fibers pass to the semilunar ganglion and are distributed with the nasal division of the fifth nerve and thence through the long ciliary nerves to the dilator.

PUPILLARY SIZE.

The size of the pupil regulates the intensity of the light incident on the retina and influences, as pointed out above (page 608), the definition of the images formed, and the depth of focus. The size of the pupil resulting, as it does, from a delicate balance of various influences is constantly changing. For any person there is an habitual pupillary size from which as a base occur the rapid reflex changes of size; both features should be kept in mind in the following discussion. The habitual size of the pupil is small in the new-born, larger in youth, reaching a maximum of perhaps 4 mm.[1] at twenty years, and thereafter is smaller again with increasing age. It is said to average larger in women than in men and in myopes than in hyperopes, but there are many exceptions.

Reactions of the Pupil.—The important reactions of the pupil, or, more correctly, the changes in size of the pupil due to reactions of

[1] It should be remembered that the pupil as seen through the cornea is magnified about one-eighth.

of the iris, are due to: (*a*) *Changes of light intensity,* (*b*) *convergence* and *accommodation,* (*c*) activities of the *autonomic nervous system* and (*d*) certain *drugs.*

The changes in size of the pupil are chiefly reflex, but in part are associated movements and perhaps in some small degree direct responses, since the iris in some animals will contract when light falls upon it even though no nervous connections are present. In man and mammals with incomplete decussation of the optic nerves the two pupils are normally of approximately the same size and react together in approximately the same degree.

Reactions to Light.—Physiologically, the most important reaction is that to light. The pupil *contracts* to an *increase* and *dilates* to a *decrease* in the *intensity* of the *light falling upon the retina.* The reflex paths are through the optic nerves, apparently to the corpora quadrigemina and thence by unknown paths to the third nucleus from which the sphincter is reached or to the lower cervical cord from which the dilator is reached over the routes outlined above. Tonic influences from both centers are commonly present, so that, for example, a constriction follows either from a stimulation of the sphincter or inhibition of the dilator.

In considering the reaction to light we must distinguish between the *immediate response* and the *final size attained.* The final, or *physiological pupillary size* for a particular intensity of light is only attained with complete *adaptation* of the eye to that intensity (page 638). When sufficient time for adaptation is allowed (for example, thirty minutes) the pupillary size is found to vary comparatively little over the considerable range to which the eye is commonly exposed. It is, however, distinctly larger for complete darkness and smaller in very intense lights, such as direct daylight. The pupillary size over a wide range of intensities is shown in Fig. 92. The areas of the pupil rather than the diameters are given, since it is the area which determines the brightness of the retinal image. This figure should be compared with that given for adaptation (Fig. 103) in which the scale of brightnesses is the same. It should be noted that the scale for the pupillary area is an arithmetical one, which gives too great an impression of change; the actual change of the pupillary area is seventeen fold, whereas the intensity of the light is altered through a billion fold.

The *immediate response,* or *light reflex,* is conditioned by the following factors: (*a*) The state of adaptation of the eye; (*b*) the portion of the retina illuminated; (*c*) the size of the retinal image; (*d*) the intensity of the light source, or, more exactly, the change in brightness from that to which the eye has been exposed. Since adaptation has not yet been discussed, it will be sufficient to state that the pupil of an eye previously in the dark or in very dim light constricts more rapidly and to a smaller size than does one pre-

viously in the light, and that lights that seem equally bright are equally effective, although in comparing a light-adapted with a dark-adapted eye these lights may be objectively different. Stimulation of the central portion of the retina gives more powerful constriction of the pupil than that of peripheral regions. This and some other evidence indicates that the pupillary responses are

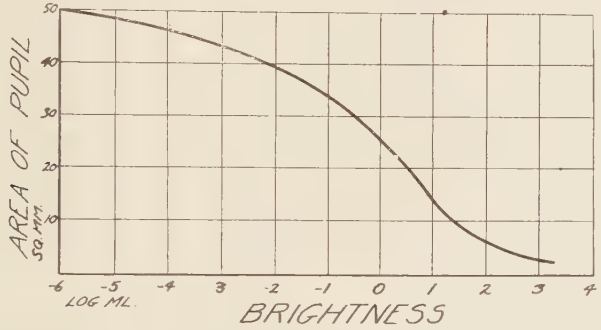

FIG. 92.—Area of pupil when the eye is exposed to different light intensities. (Data from Reeves and Holladay.)

initiated in far greater degree by the cones than by the rods. It is also claimed that these reflexes involve different fibers than those giving rise to sensations. The size and change of brightness of the object are so related that increased brightness compensates for decreased size, that is, that the product of the area and the brightness producing a response tends to be constant. It is interesting

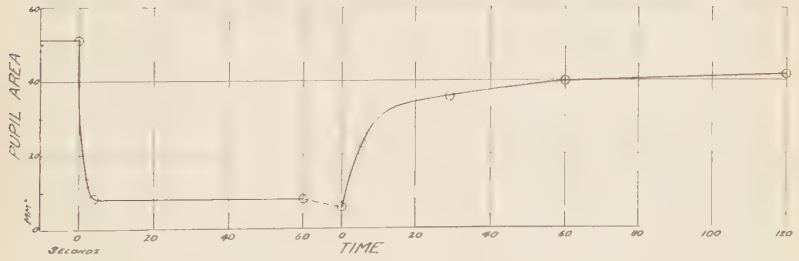

FIG. 93.—Rate of closing and opening of the pupil. (Reeves.) The left hand time scale reads from the turning on of the light, the right hand from its turning off.

to note that the least change of light intensity causing a change in the pupil is very closely that which the person can distinguish subjectively. The effectiveness of colored lights agrees with their subjective brilliance, that is, the extent of the response to different wave lengths is proportional to the visibility values shown in Fig. 102.

The immediate response of the iris to change of illumination is rapid, the exact course varying with the extent and direction of the change. The closing to an increase of light is far more rapid than the opening to a decrease, and the closing or opening is more rapid the greater the change of light intensity. If the change in intensity is slight the change in the size of the pupil is followed by a return to the original size. With greater change in the light the pupil returns to the physiological size, which it at first overshoots, for the final intensity. When the change of illumination falls below a certain rate no alteration of the pupil occurs, adaptation keeping pace with the shifting intensity over a moderate range.

Associated Movements of Pupil.—Normally in looking at a near object accommodation, convergence of the eyes and constriction of the pupils occur together and are referred to as *associated movements;* it seems probable that their relation is that of *conditioned reflexes* (page 723). The pupillary changes are primarily related to convergence rather than accommodation.

Activities of those sections of the autonomic system connected with the sphincter and dilator lead to constriction or dilation of the pupil. Thus, in fear, involving extensive sympathetic thoracicolumbar activity (page 735), the pupils are dilated.

Drugs which affect the autonomic endings will, of course, affect the pupil. Thus atropine and homatropine cause dilatation of the pupil by paralyzing the stronger sphincter as well as failure of accommodation by paralysis of the ciliary muscle. On the other hand, eserine and pilocarpine cause forced contraction of the sphincter and of the ciliary muscle. Adrenin causes dilatation by stimulation of the dilator.

Summary.

The eye in man and the higher vertebrates represents probably the most highly specialized receptor. It is the chief distance receptor in man and other primates and in birds, and sight is for them the dominant sense.

The stimulus is *light* or *visible radiation;* this has the power of causing in certain tissues photo-chemical changes and thus alteration of functional metabolism. The retina is such an organ, and this and Chapter XXXVI are devoted to the physiology of the retina and its accessory structures. The visual organ thus consists of a bulb containing a layer of photo-sensitive cells and the accessory apparatus required for the formation of images on this sensitive layer and attached to this bulb the muscular mechanism accomplishing the many accurate movements involved in vision. In addition, there are means of maintaining the nutrition of the bulb and insuring the protection of an organ that is necessarily placed in a prominent position.

The structures of the eye may be classified as follows:

A. Essential receptors, the retina or more exactly the rods and cones.

B. Accessory structures.

(*a*) An *image-forming apparatus*, including all parts contributing to the formation of images.

1. All *media traversed by light*, tears, cornea, aqueous humor, lens, vitreous body and most of the retina.
2. Apparatus for *focussing*, including the lens, suspensory ligament, ciliary muscle.
3. *Light-excluding* structures, sclera and the pigments of chorioid, iris and retina.
4. *Light-regulating* apparatus, the iris (and migratory retinal pigment in certain animals).
5. Mechanism for *preserving position* of parts of *optical system*, sclera and intra-ocular pressure.

(*b*) *Directive apparatus*, orbital fat, muscles, fascis bulbi, check ligaments and associated structures.

(*c*) *Protective apparatus*, orbit, lids and lashes, eyebrows, lachrymal apparatus.

(*d*) *Nutritional apparatus*, structures involved in production and circulation of aqueous humor.

The stimulus for the eye, *visible radiation*, consists of a small range, approximately one octave, of electromagnetic frequencies. These have the maximal physiological effect (for the light-adapted eye) at about 556 μ and but $\frac{1}{100}$ of this at 408 μ and 720 μ.

Sunlight is our ordinary standard of mixed frequencies and is duplicated only by sources having a high temperature. Light is propagated through air at a velocity of 300,000 km. per second and through other transparent media at somewhat lower rates. Its propagation is so regular and predictable that its study constitutes an entire branch of physics, called geometrical optics.

Visible radiation traversing a medium and encountering a body may be *transmitted* and usually changed from its course or *refracted*, it may be *absorbed* or *reflected* or it may suffer, in part, all three fates. For the formation of images refraction through lenses is the most important feature of geometrical optics. A *lens* is a portion of an isotropic transparent substance bounded by polished faces of regular geometrical form, one of which may be a plane.

Light incident on a convex lens (a lens thicker at the center than at the edges) from a point will be concentrated at a second conjugate point or focus in the opposite side of the lens. When the point source is infinitely distant the conjugate point is the *second focal point*, the distance of which from the center of the lens is the *focal distance*. The totality of the conjugate points corresponding to

the objects before a lens constitute an image. The refractive power of a lens is measured in *diopters* and is equal to the reciprocal of its focal distance in meters.

Refraction in the eye occurs at the surface of the cornea and at the two surfaces of the lens. Because of the greater difference in refractive index between the air and the cornea the greater part of the refraction takes place here.

Since the tracing of the rays of light through the eye is a complex problem, it is customary to substitute in calculations a less complicated "schematic eye" based on average measurement or a still simpler "reduced eye." The reduced eye of Donders is sufficiently accurate for most purposes and is easily remembered because of the round numbers. It consists of a single medium of the refractive index of water ($\frac{4}{3}$) separated from the air by a "cornea" with a radius of 5 mm. The center of curvature of the cornea which is also the nodal point is 15 mm. from the retina, which is at the second focal point. The first focal point is 15 mm. in front of the cornea.

The refractive power of the eye may be so altered that the images of objects at different distances will fall in the retina. This process is called *accommodation*. This is affected by changes in curvatures of the surfaces of the lens. At rest the eye is accommodated for distant objects; the lens is then under tension from the suspensory ligament and the surfaces are the least curved. In accommodating for near objects the ciliary muscle contracts; the origin from the sclera near the base of the cornea remains fixed; the chorioid into which it is inserted is stretched and the ciliary processes to which the suspensory ligament is attached are moved forward and toward the optical axis. In consequence the tension on the lens is relaxed and the elasticity of its capsule leads it to become more convex.

The point conjugate to the retina without accommodation is the *far point;* the point conjugate to the retina with maximum accommodation, the *near point*. The *amplitude of accommodation*, or *degree of alteration of the refractive power of the eye* is given by the formula:

$$A = \frac{1}{fp} - \frac{1}{np}$$

A, amplitude; fp, far point distance in meters; np, near point distance in meters, both distances being negative.

The amplitude decreases with age.

The optical system of the eye shows spherical, chromatic aberration and similar imperfections found in other lenses, but the most important defects are those arising from disparity between the refractive power and the distance of the cornea and lens from the retina. When these are so related that the *second focal point of the unaccommodated eye falls in the sensitive layer of the retina* or the

far point is infinitely distant the condition is called *emmetropia*. Any deviation from this condition, which usually takes the form of too long or too short a bulb, is called *ametropia*. *Myopia* is that form of ametropia in which the *second focal point of the unaccommodated eye falls in front of the sensitive layer of the retina* or in which the *far point lies at some finite distance from the eye* (in practice less than the 6 m. or 20 feet used in testing). The *near point* will be *closer* to the eye than in emmetropia with equal amplitude of accommodation. A concave lens giving to parallel rays a degree of divergence equal to those coming from the far point will permit distant objects to be imaged on the retina.

Hyperopia (hypermetropia) is that form of ametropia in which the *second focal point of the unaccommodated eye lies behind the sensitive layer of the retina*. There is, therefore, *no real far point. A virtual far point,* representing the point of intersection toward which light is converging, exists; this lies behind the eye. The near point is more distant than in emmetropia of the same amplitude of accommodation, since part of the accommodation is expended in causing parallel rays to be focussed in the retina and less is left to converge the light from still nearer objects. A convex lens giving to parallel rays the convergence corresponding to the *virtual far point* will permit distant objects to be imaged in the retina.

Astigmatism (astigmia) is a defect in which different meridians do not show the same degree or kind of ametropia; one meridian may be emmetropic and the other hyperopic or other combinations. It usually results from unequal curvature of different meridians of the cornea, of which the vertical is commonly the more curved. The correcting lens must include a cylindrical element which brings all meridians to the same refractive power.

Presbyopia is the condition of the eye accompanying increasing age in which the amplitude of accommodation is insufficient for reading or other near work.

The iris is important because of its effect on the image formation of the eye and its unexpectedly intricate nervous control which makes its reactions significant in diagnosis.

It contains two antagonistic smooth muscles, the sphincter and the dilator. The sphincter is innervated from the cranial and the dilator from the thoracico-lumbar section of the autonomic system.

The size of the pupil affects the intensity of the light incident on the retina, the definition of the images formed and the depth of focus.

For any person there is an habitual pupillary size which changes with age, being small in childhood, increasing to a maximum at about twenty years and thereafter decreasing. The reactions of the iris are due: (*a*) To *changes in light intensity*, (*b*) to *convergence* and *accommodation*, (*c*) to activities of the *autonomic nervous sys-*

tem and (*d*) to certain *drugs*. The pupil *contracts* to an *increase* and dilates to a *decrease* in the *intensity of light* falling on the retina. Over a considerable range of ordinary intensities the final size is practically constant; to this size it returns after each change in intensity as the retina becomes adapted to this new level.

With convergence and accommodation contraction of the pupil occurs. Activities of parts of the autonomic system lead to activities of the connected muscles of the iris; thus in fear, involving extensive discharges from the thoracico-lumbar portion, the pupils are dilated.

Drugs which affect the autonomic endings will affect the pupil. *Atropine* causes *dilatation* by paralyzing the sphincter (and failure of accommodation by paralyzing the ciliary muscle); *eserine* causes *constriction* by stimulation of the *sphincter; cocaine, dilatation* by stimulation of the dilator.

For bibliography see end of Chapter XXXVI.

CHAPTER XXXVI.

VISION: SENSATION.

THE RETINA.

Having considered the process of image formation we are in a position to take up the response of the retina to such images. Since the retina shows marked regional differences in structure which are reflected in the character of the responses obtained from these regions, it will be necessary to recall the anatomy already presented (page 585) and to discuss certain additional features. If the retina is traced forward from the posterior portion of the bulb, where it presents its typical structure, it is found to diminish

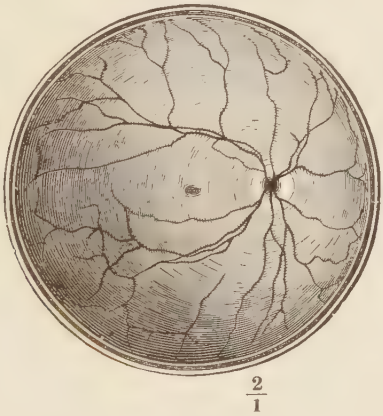

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Fig. 94.—The retina of the right eye seen from the front, the anterior half of the bulb having been removed. The white spot with the bloodvessels radiating from it is the optic papilla; the dark spot to the left of this the foveal region. (Martin's "Human Body," Henry Holt & Co., Publishers.)

gradually in thickness from about 0.4 mm. to approximately one-fourth of this at a point 5 or 6 mm. from the base of the iris. Here at the *ora serrata* there is an abrupt transition visible to the naked eye and the retina loses its complex structure and is reduced to a thickness of about 0.025 mm. Anterior to this, the retina is represented by a layer of elongated columnar cells and a continuation of the pigment layer, already noted as extending to the pupillary margin. That portion posterior to the *ora serrata* is alone sensitive to light and is the portion meant by the term retina, as this is ordinarily used.

Regional Differences of Structure.—Certain regions of the retina require separate consideration; these are the *papilla* of the *optic nerve* (*optic disk*), the *macula lutea* and the *fovea centralis*. The *papilla* is the point of exit of the fibers of the optic nerve, which, having converged from all parts over the inner surface of the retina to this point, turn outward and pierce the remaining layers of the retina, the chorioid and the sclera to pass to the brain as the optic nerve. In consequence, all elements of all layers, except the nerve fibers, are absent at this point. As seen with the ophthalmoscope the optic disk appears white, since the axons of the ganglion cells first become medullated as they pass outward through the layers of

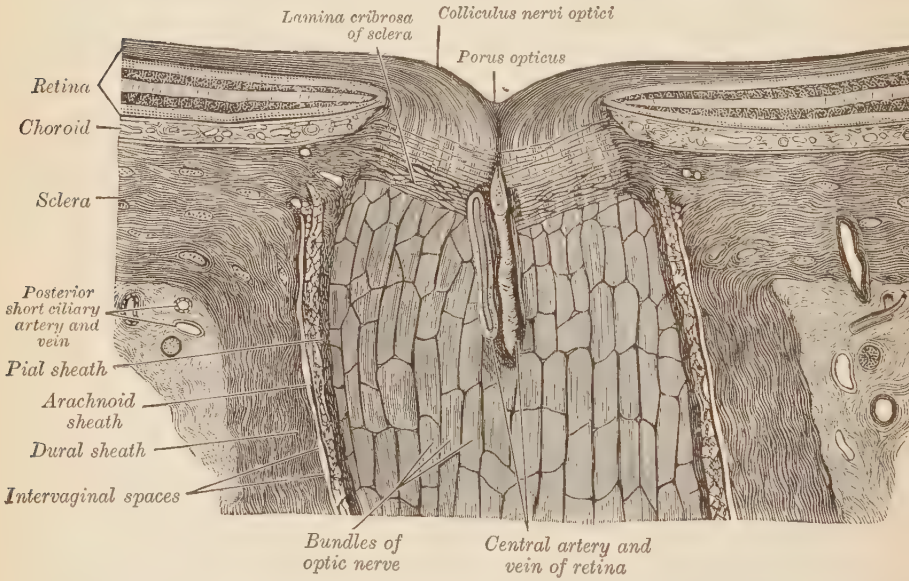

Fig. 95.—The terminal portion of the optic nerve and its entrance into the eyeball, in horizontal section. (Toldt.)

the bulb. The optic disk is about 1.5 mm. in diameter and lies approximately 3 mm. medially (nasally) and 1 mm. below the posterior pole of the eye, although there is considerable individual variation.

Approximately on the axis of the bulb lies an extremely important region marked by several features. One is the presence of a yellow pigment distributed over an area called, because of this color, the *macula lutea*. A second feature is the presence of a small pit or depression, the *fovea centralis*, so marked as to have been considered by some of the early anatomists a hole through the retina. It is shown in Fig. 94. A third feature is the absence of rods over a

space which is therefore known as the *rod-free area*. This peculiarity has been established by histological examination and may be demonstrated subjectively, but cannot be seen with the ophthalmoscope. Lastly, the retinal circulation is also absent from a small *non-vascular area*.

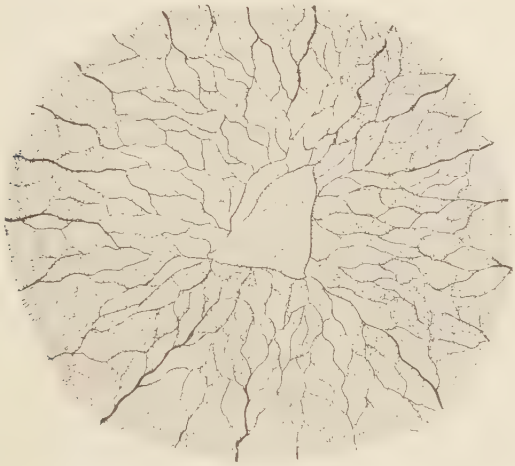

FIG. 96. –The vascularization of the macular region with the central non-vascular region as seen entoptically. (Randall.) (de Schweinitz, "Diseases of the Eye," W. B. Saunders Co., Publishers.)

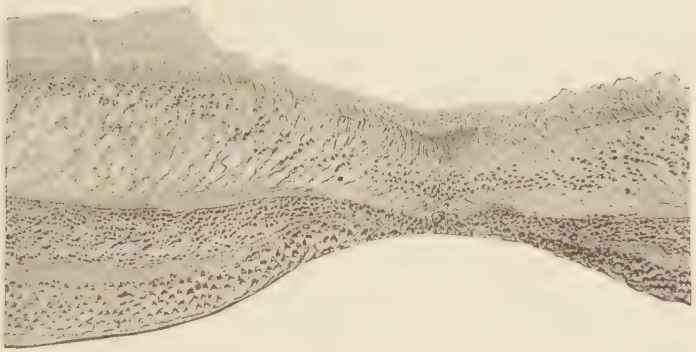

FIG. 97.—Photograph of section through the fovea. (Golding-Bird.) The vitreous would lie below, the chorioid above. (From Schäfer's "Essentials of Histology," by permission of the author.)

This region briefly characterized by all four of these features was called by Helmholtz "the most important part of the entire retina for vision." Unfortunately different investigators have given very different dimensions for these areas, a result of the difficulty of

obtaining satisfactory material and probably also of individual differences. The macula lutea is apparently the largest and most variable of the areas; within this are included in descending order of size the rod-free area and the fovea centralis. The non-vascular area has been less carefully measured and its size is of less moment.

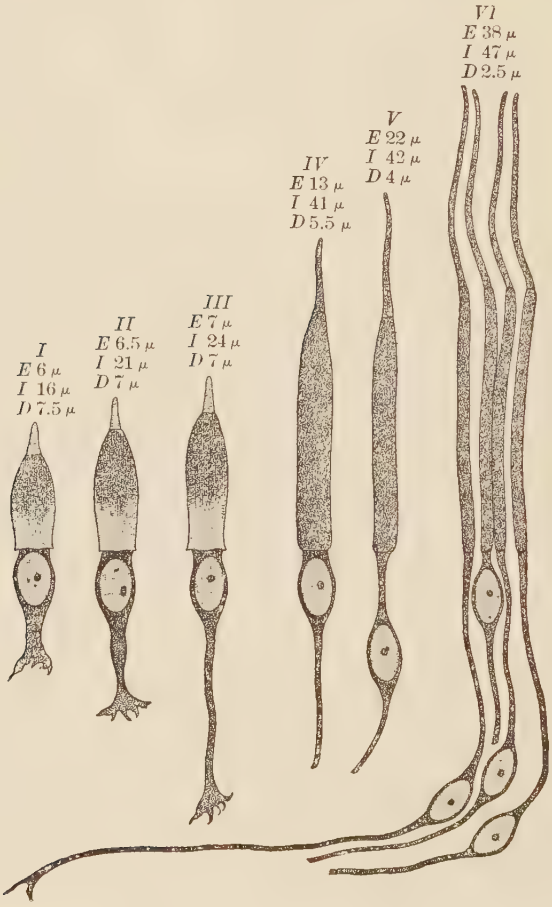

FIG. 98.—Cones from different regions of the retina. (Greeff.) *I*, from near the ora serrata; *II*, from 2 cones farther back; *III*, from the equator; *IV*, from the periphery of the macula lutea; *V*, from near the margin of the fovea; *VI*, from the center of the fovea. Above each is given; *E*, length of outer segment; *I*, length, and *D*. diameter of inner segment. (Gray's Anatomy, Lea & Febiger, Publishers.)

The macula is the only one for which measurements exceeding 1 mm. are given; the figures for the rod-free area range from 1 mm. down to about 0.5 mm., while the fovea is usually given as 0.4 to 0.2 mm., although figures as large as 1 mm. occur. According to

most observers, all these areas are horizontally oval. The center of the fovea is characterized not only by the absence of rods, but also of bipolar and ganglion cells which lie at or near the margins of the pit, whence they connect obliquely with the cones. It is possible that the rod-free area rather than the fovea is the most significant physiologically.

The Neuroepithelium.—The various types of essential retinal structures exist in very different numbers and show regional differences in form and arrangement. The elements of the neuroepithelium, the rods and cones, outnumber all other kinds of cells. The rods have been estimated at from 65,000,000 to 130,000,000; they are absent, as stated, from the rod-free area; over the remainder of the retina they are fairly uniform in size. The cones are less numerous, being estimated at 3,500,000 to 7,000,000, and are less uniform in their distribution and size. In the fovea they are long and slender, measuring about 2.5 μ in diameter, and the outer segment is nearly as long as the inner, so that in form they are suggestive of rods. Passing peripherally they become progressively less numerous until near the ora serrata cones are only occasionally found. At the same time they become shorter and thicker, especially the inner segment which may measure as much as 7.5 μ in diameter, and is here two or three times as long as the outer segment.

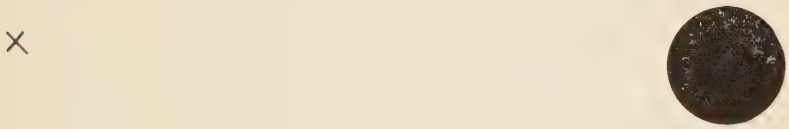

FIG. 99.—Blind spot. Close or cover left eye, fix right on cross and move page to and fro; at 30 to 35 cm. the spot will disappear.

The neurons of the second order, the bipolar cells, are fewer, numbering about 90,000,000, while the fibers of the optic nerve, and hence of the ganglion cells, number but 400,000 or 500,000. It is thus clear that on the average between 100 and 200 rods or cones must converge on one nerve fiber. Concerning the actual mode of connection we have few data except for the fovea, in which both anatomical and physiological evidence indicates a one-to-one relation of cones and central pathways.

Rods and Cones the Receptors.—The histological relations indicate that the rods and cones are the receptors. This is supported by physiological evidence. They are absent from the region anterior to the ora serrata and this portion is insensitive to light. They are absent from the optic disk, the fibers of which, as in the case of other nerves, do not respond to light. The insensitivity of the optic disk which leads it to be called the "blind spot" is easily demonstrated (Fig. 99). Under appropriate conditions the shadows of the

retinal bloodvessels can be seen, showing that the sensitive elements are behind the vessels. These shadows known as Purkinje's figures are well demonstrated in the dark room by concentrating the light from a small lamp on the sclera and keeping the point of light in constant motion. If the light point is shifted the shadow also moves; by measuring the extent of movement of the light and shadow it is possible to calculate the separation of vessel and sensitive layer. Such calculations agree with the known separation of the vessels and the rods and cones. Lastly, as we shall later discover, the size of the foveal cones agrees with the fineness of detail that can be distinguished. We may thus safely conclude that the rods and cones are the essential receptors.

OBJECTIVE CHANGES ON STIMULATION.

When visible radiation of proper intensity falls upon the retina photo-chemical (or photo-electric) changes are set up leading to modifications of functional metabolism and eventuating in reflexes or sensations. In contrast to the manifold sensations and reflexes, the number and extent of demonstrable objective changes are surprisingly small. They may be grouped as follows: (*a*) *Structural changes* that may be shown on histological examination, (*b*) changes involving *visual purple* and (*c*) *electric changes.*

The structural changes appear not to be significant for man. Migration of the retinal pigment which invades the layer of rods and cones in the light and recedes from it in the dark, and changes in the length of the cones, can be shown in lower vertebrates, but have not been conclusively demonstrated in mammals, and if present must be of negligible importance. Prolonged exposure to light changes the staining reaction of the retinal elements, but this appears to be a general fatigue effect which at present does not help us to understand vision.

The changes of visual purple and the electromotive responses promise more insight into the visual processes but are slight in amount, and because of the difficulties which they present have been incompletely investigated.

There is present in the retina of man and of most vertebrates a purplish or rose-colored substance; called visual purple or rhodopsin, that bleaches on exposure to light. It seems to be associated with the rods being absent from eyes lacking rods, as in some snakes, and from the *fovea centralis.* Its absence from the fovea has been disputed and is difficult to establish because of the minute size of these parts.

It is a photo-labile substance of unknown chemical nature which can be isolated and tested *in vitro.* Its color is due to a greater absorption of green and yellow rays, allowing an excess of blue and

red to reach the observer's eye. As might be expected from this, it bleaches most rapidly when exposed to yellow-green light (about 510 mμ for the frog). The curve representing the rapidity of bleaching agrees very closely with that for the relative brilliance (brightness) of a dark-adapted eye. (See Fig. 100.)

If absent from the fovea it is not essential to daylight vision, but there is evidence that it is more important in dark adaptation. More knowledge of its nature and the changes which it undergoes in the living eye is highly desirable.

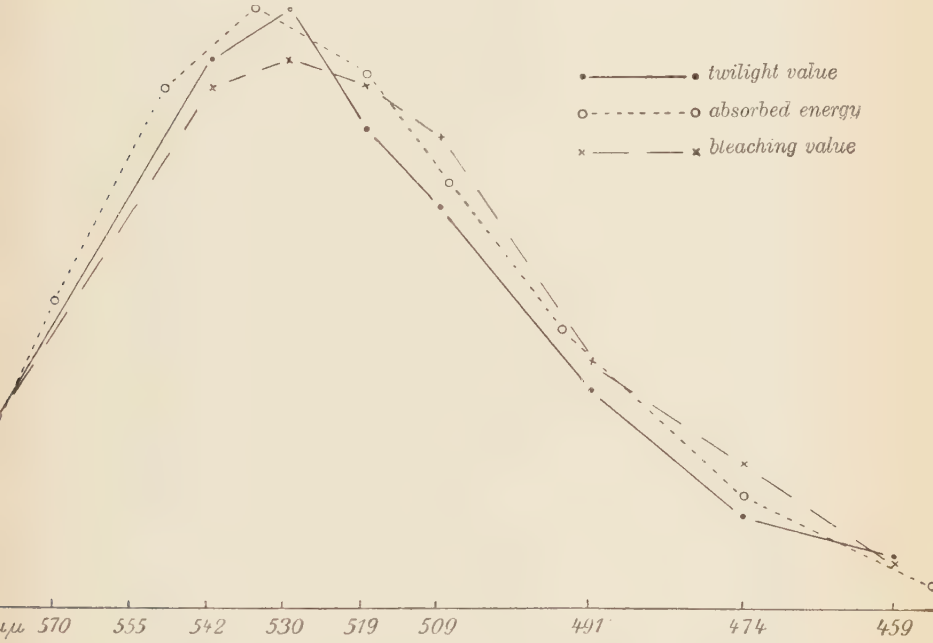

FIG. 100.—Visibility in dim light compared with properties of visual purple. (Helmholtz Physiological Optics edited by J. P. C. Southall, Optical Society of America, 1924, vol. ii, p. 388, Fig. 72. (Printed by George Banta Publishing Company, Menasha, Wis.)

The electromotive changes are also of great interest. If a highly sensitive galvanometer is connected with the cut optic nerve and the cornea or the inner surface of the retina a difference of potential will be observed, the optic nerve being negative with respect to the anterior part of the bulb. When light is admitted to the eye rapid changes of potential occur which differ in detail with the intensity and duration of the light and the state of the eye.

If this procedure measures the action current of the optic nerve, as we have reason to believe it does, there should be a parallelism

between the electromotive effects and the sensations or reflexes that follow specified stimuli. Should a satisfactory parallelism be established the electromotive response of the eye would furnish a check on a great variety of complex responses known only through difficult introspection and might greatly increase our understanding of vision.

Either an increase or a decrease of light, if rapid enough, causes an electromotive response which, though not the same in detail, indicates that either "light" or "darkness" constitute stimuli. The range of frequencies evoking electromotive responses is approximately that visible to the eye and the maximum response is obtained from the frequency which is very near that appearing brightest to the eye. The threshold for the electromotive response is not far from that for vision. It has also been pointed out that the time relations of the electromotive response parallel very closely those of light sensations in the case of a flash of light on a dark-adapted retina. The relation between the intensity of the light and the difference of potential shown by the eye strongly suggests the relation between the light and the sensation. It is probable that the further application of modern electrical methods to this problem will help to elucidate the mechanism of vision.

VISUAL SENSATIONS.

The visual sensations present richness, variety and complexity unequalled by any other receptor. These sensations early attracted scientific attention. Many able men have labored at describing and organizing them, however, the task has proved so difficult that no final agreement has yet been reached.

Attributes of Visual Sensations.—Any visual experience may be completely characterized by a short list of attributes, some of which are primary attributes of sensation and some are more complex, being attributes of percepts to which other receptors than the retina contribute. Although these attributes are not independent but complexly interrelated, their enumeration may serve as a basis about which to group discussions of special features of particular interest. The primary attributes peculiar to visual sensations or sensations of *color* (using this term to include all retinal sensations) are *brilliance*, *hue* and *saturation*. It is important that these terms are recognized as representing psychological entities and not confused with physical attributes of the visual stimuli with which their relations are complex.

Brilliance (also called luminosity and brightness) is an attribute of color best illustrated by reference to a series of grays passing from black to white. The white end of such a series would be the most brilliant and the black end the least brilliant. Any color may

be matched in brilliance with some gray of this series by the use of appropriate methods.

Colors of the same brilliance may be divided into two series—the *achromatic*, or grays, and the *chromatic*, or hued colors. The chromatic or hued series may be so arranged that we may pass without abrupt transition from hue to hue, as from spectral red through orange, yellow, green to blue and from this through the extraspectral purples back to red. The differences presented by

FIG. 101.—Psychological color solid (Jour. Op. Soc. of America, Aug. 1922. George Banta Publishing Co., Menasha, Wisconsin.)

such a series are differences of *hue*, and the series as a whole differs from the gray series in possessing hue.

Saturation is an attribute of colors having hue that determines their degree of difference from grays having the same brilliance. By a series of steps we may pass from any hue through lesser and lesser degree of saturation to a gray of the same brilliance which may be considered to have zero saturation and hence no hue.

Since the attributes of brilliance, hue and saturation peculiar to

visional sensation are three in number a diagram of their relationship will form a solid, the *psychological color solid*. Following Troland we may, as in Fig. 101, represent brilliance along a vertical axis and hue and saturation in a plane perpendicular to this. The vertical axis may be considered as formed of a series of gray sensations graded from the darkest "black" at the bottom to the most brilliant "white" at the top. At any level of brilliance, hue and saturation may be represented in a plane; hues, corresponding to their cyclic character, being arranged in a series about the periphery while saturation is represented by the distance from the central brilliance axis representing no saturation.

Any visual sensation may also show *extensity* and *duration*, which do not differ from the similar primary attributes of other sensations.

Visual in common with other sensations show position in time; this feature requires no special comment. Certain special temporal relations of the sensation to the stimulus will be discussed with other features of the sensation. The spatial relations of visual sensations and percepts are particularly important, being more detailed and exact than those of other sensations, although not of the primary nature of the muscle sensations. Features of spatial relations are *direction*, *distance* (involving the complex relations of binocular vision), *form* and *motion* (this also involves temporal relations). We will discuss first the physical factors of the stimulus and the physiological states of the receptor that affect *brilliance* (including here certain of the temporal relations), next *chromaticity* (covering *hue* and *saturation*), then the *spatial relations*, first, as they involve a single retina (*monocular spatial perception*, *direction*, *form* and *motion*) and last *binocular spatial perception*, including distance.

BRILLIANCE.

Dependence of Brilliance on Nature of Stimulus.—The brilliance of a color varies with the physical intensity or brightness of the stimulus if the physiological state of the retina is constant. This is generally recognized, but it is also true that the brilliance varies with the frequency or wave length. It has been pointed out that different frequencies are not equal in their effect on the retina, but may be evaluated in terms of "visibility" (page 590) with a maximum at a wave length of about 556 mμ. This visibility represents the effect on brilliance. That the brilliance does not correspond to the energy contained in these spectral frequencies is clear. If the visibility curve (Fig. 102) for daylight is compared with the energy distribution of sunlight it will be seen that in passing from the maximum the retinal effect has entirely disappeared at a point where the total energy has been but slightly reduced and in the spectrum from ordinary sources of light the visibility is less at

a point near the red end of the spectrum at which the energy is rising rapidly.

In addition to the intensity and frequency of the stimulus, other features affect brilliance. To be visible, that is, to show a just perceptible difference in brilliance from its surroundings, the stimulus must have a certain duration, area and intensity. These three features are so related that within certain limits an increased area or an increased duration will compensate for a reduced intensity; the description of the stimulus must include these three features, although area might more justly be considered as a retinal factor.

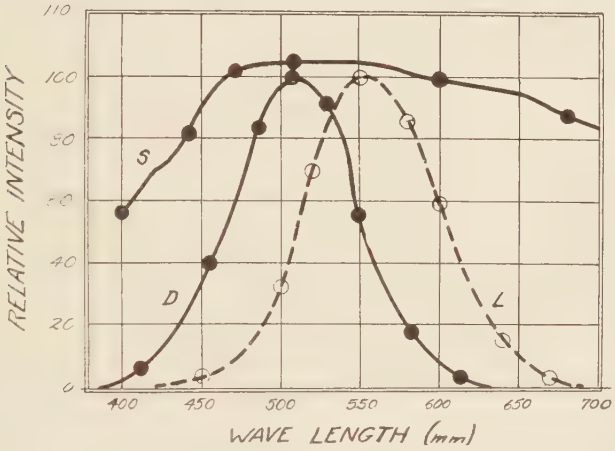

FIG. 102.—Visibility for the light adapted eye (*L*), and for the dark adapted eye (*D*), and relative intensity of noon sunlight (*S*). (Data from Troland, Hecht, and Abbot.)

Dependence of Brilliance on State of Retina.—We have thus far assumed the brilliance sensitivity of the retina to be constant, but this is far from being the case.

The effect of a given physical stimulus will vary widely with: (*a*) The region of the retina upon which it falls; (*b*) the previous history of this part of the retina, that is to say, with the stimuli to which it has just been exposed and with (*c*) the stimuli acting simultaneously on other and particularly adjacent parts of the retina. The first two of these will be discussed under the head of *adaptation;* the last under *contrast.*

Adaptation.—It is a common experience that the eye varies greatly in sensitivity accordingly as it has been in the dark or light and that the process of "becoming accustomed" or *adapted* to light or dark, as when we pass from a brightly lighted room into the night or from a tunnel into the sunlight, takes a certain time. To appreciate the

extent and usefulness of the changes involved in adaptation we must consider the range of physical intensity under which the eye must function. In bright sunlight the eye encounters brightnesses as high as 2500 ml.[1] Indoors in the evening by artificial light sufficient to read with complete comfort the brightness may be 5 ml. Outside on a starlit but moonless night we may get about without difficulty, although we cannot see fine detail with a brightness of 0.001 ml.

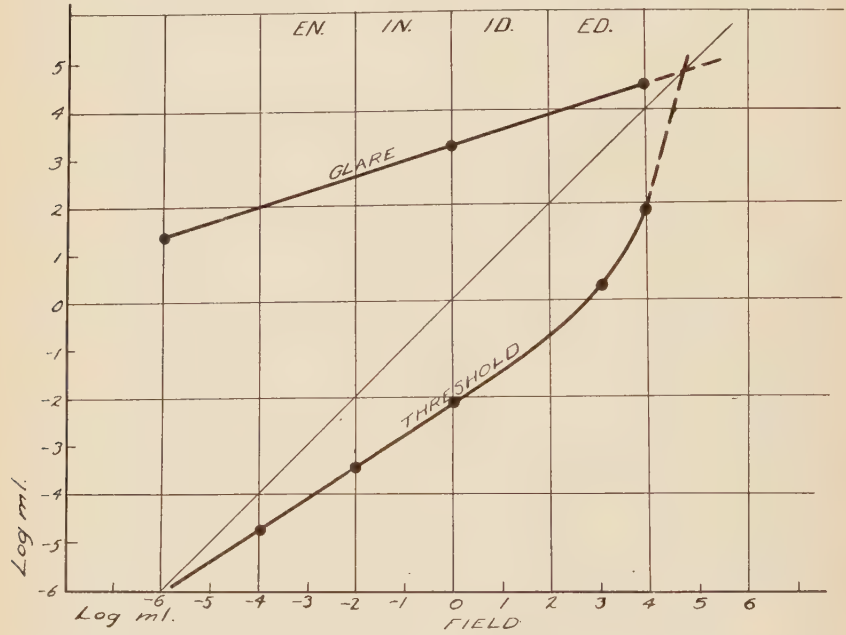

FIG. 103.—Threshold and glare values for different states of adaptation. (Data from Nutting.) Below is shown the brightness to which the eye is adapted, on the left the brightness that can just be seen or which is unpleasant. *EN* indicates the approximate brightness of outdoors at night; *IN*, interiors at night; *ID*, interiors by day; *ED*, exteriors by day.

We thus normally use our eyes, though, of course, not with equal efficiency, over the enormous range of brightness of two or three million fold. In some persons this power of adaptation is defective and such night-blind individuals are nearly helpless at night, since they cannot avoid obstacles easily seen by those with normal vision.

When the eye has been exposed for thirty to fifty minutes to a particular intensity of light it may be said to be *adapted* for that intensity. For this level of adaptation the threshold or least inten-

[1] See page 590 for photometric definitions.

sity that can immediately be distinguished from complete darkness may be found. An upper limit of tolerance, recalling that of the ear, may also be found, although the brightness limit is here called "glare." In Fig. 103 are shown the thresholds and glare values thus

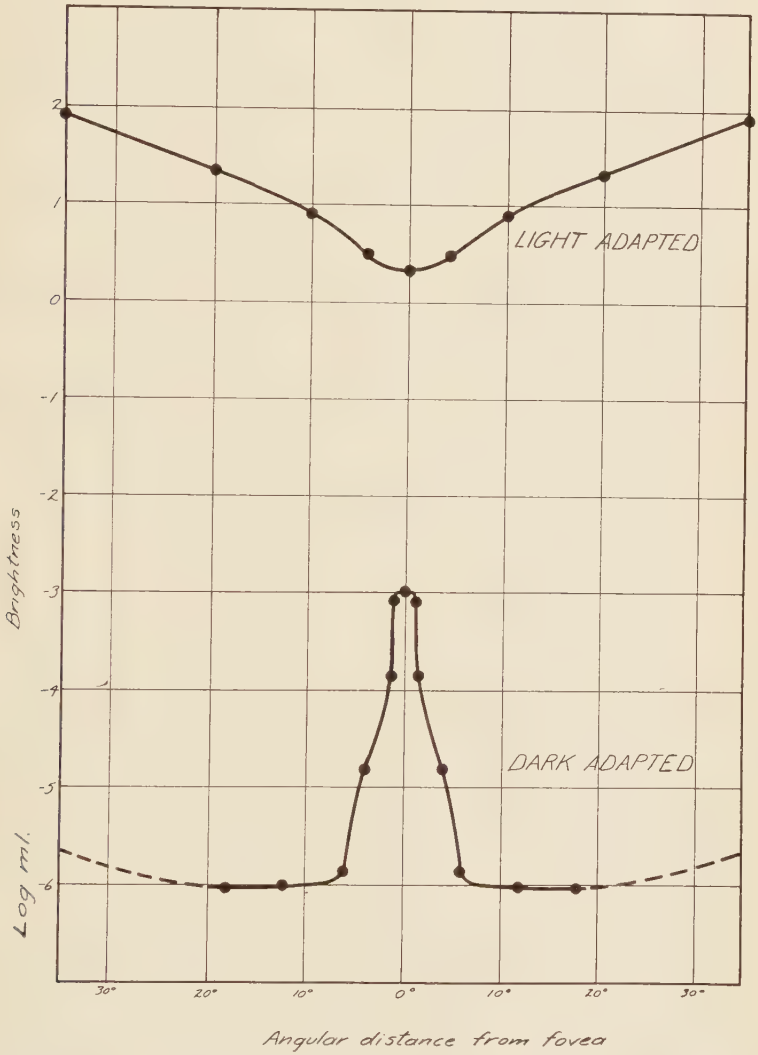

FIG. 104.—Thresholds of various regions of the light and dark adapted retina. (Data from Nagel, Brewer, Pertz, Vaughan and Boltunow.) (See text.)

determined for a wide range of intensities. Because of the enormous changes involved both scales are logarithmetic. A number

of features are worthy of comment. The range of experimental intensity which the eye can endure, and under which it can give consistent results is from 10^{-6} ml. (one-millionth) to 10^{4} ml. (ten thousand), a variation of 10^{10}, or ten billion fold. This is far in excess of the variation in brightness given above as normally encountered. With the greatest brightnesses the threshold is nearly 10^{8} (one hundred million) times that for the weakest light. So great is the utility of this range of threshold to animals exposed to the light variations of day and night that we never fully appreciate the extent of the change in our surroundings. Even the value of glare is altered a thousand fold, illustrated by the fact that an automobile headlight painfully bright at night will pass unnoticed in the day. Greater intensities, such as are found in the electric welding arc or the sun, lead to injury of the retina.

In determining these figures large areas of the retina were used, but in reality the sensitivity of all parts of the retina is not the same. In the light-adapted, or *photopic*, eye the fovea has the lower threshold and in passing peripherally the stimulus must be greatly increased, for example, forty fold at a distance of 35 degrees. In the completely dark-adapted, or *scotopic*, eye, on the other hand, the fovea is the least sensitive region. This may readily be observed in the evening as the stars begin to appear, when a faint star that can just be seen out of the "tail of the eye" will, if directly observed, disappear in the less sensitive fovea.

Changing from ordinary condition of daylight vision to complete *scotopic*, the foveal, or, more exactly, rod-free area, has increased over a thousand fold in sensitivity, but this is so far surpassed by the adaptation of the periphery which has increased one hundred million fold that it now appears as a relative scotoma or blind spot requiring one thousand times as much light as does a point 15 degrees distant. In fact an intensity readily stimulating the periphery but not the rod-free area may be offered by the ceiling in the early morning when the eyes are dark adapted or by the twilight sky and in looking at these the unstimulated foveal region will appear as a dark area, a phenomenon known as Maxwell's spot. The thresholds for various regions of the eye are shown in Fig. 104.

Course of Adaptation.—The course of adaptation (the change of threshold with time) presents a number of interesting features. It varies with the region of the eye tested, with the level of external brightness from which the process is started, and whether the brightness is decreased or increased. The condition most commonly studied is the decrease of threshold following a change from bright surroundings to darkness, called dark adaptation. The threshold plotted against the time in the dark is shown in the left-hand part of Fig. 105. If the process is reversed by passing from the dark into the light, the threshold is found to rise more rapidly than it fell.

Although "getting used" to the light is clearly a more rapid process it has been less studied than dark adaptation; one of the determinations is given in the right hand part of the figure.

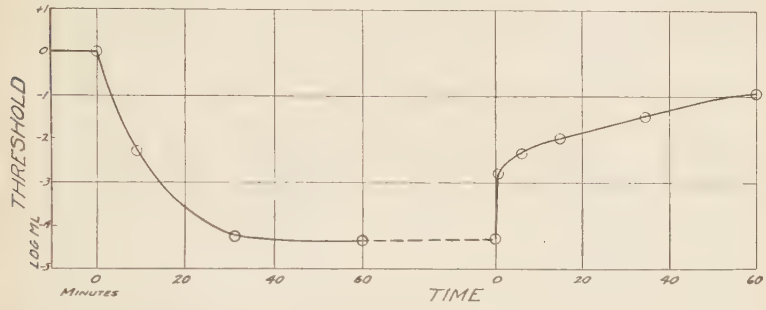

FIG. 105.—Course of dark and light adaptation (peripheral). From left to right are given the successive thresholds when the light is turned off and later turned on.

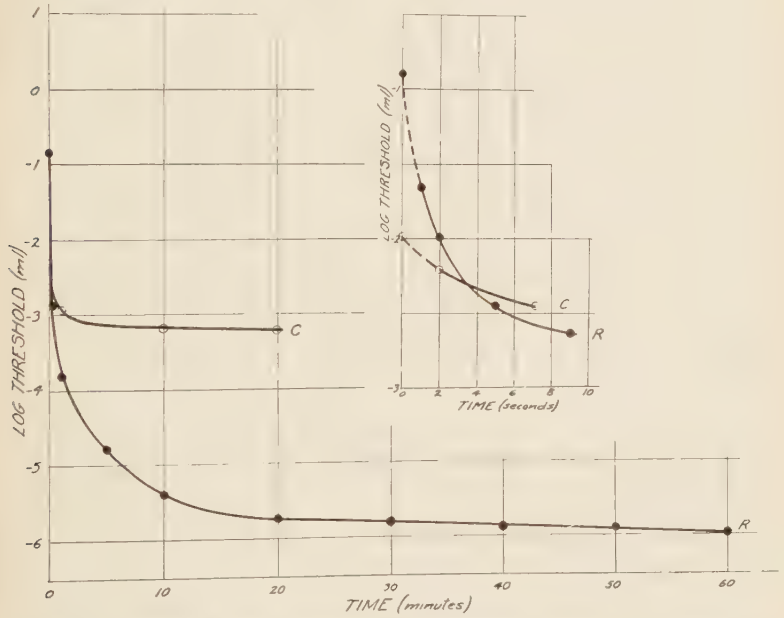

FIG. 106.—Course of dark adaptation. The successive values of the threshold for the periphery (*R*) and the rod-free area (*C*) are shown above the time. The inset shows the detail up to the crossing of the curves on an enlarged scale. (Data from Blanchard (*R*) and Hecht (*C*).)

All the thresholds represented in the figure were obtained by allowing the observer to use the most sensitive part of the retina, which as we have seen would be the central portion in bright and the peripheral part in dim lights. If the observations are confined

to the foveal or more strictly rod-free area, the course of adaptation is different. It is commonly stated that foveal adaptation is absent or negligible. Although the range is far less than at the periphery, the threshold nevertheless decreases over a thousand fold in dark adaptation as shown in Fig. 106. The rapidity of the change and the difficulty of restricting the observations to the minute rod-free area which is about 0.8 mm. in diameter are undoubtedly responsible for the usual negative results. A comparison of the course of foveal dark adaptation (line "*C*") with that of the periphery ("*R*") is interesting. Up to about four seconds it outruns the peripheral decrease of threshold, but it is practically complete in ten minutes, whereas the periphery continues to increase in sensitivity up to at least an hour.

Purkinje's Phenomenon.—Certain other differences between the photopic and the scotopic eye should be noticed. In discussing the visibility of different frequencies, the values presented were those of the light-adapted eye. If these are determined for the dark-adapted eye using a spectrum of low intensity a visibility or brilliance curve of the same shape is obtained but displaced, so that the maximum lies at a shorter wave length, about 520 mμ (see solid curve, Fig. 102). The most brilliant hue thus shifts with a change from light to dark adaptation, from the yellow into the green; this is known as Purkinje's phenomenon. A familiar example of this phenomenon is seen in matching red and blue paper or cloth for brilliance. Such a match made in the daylight is no longer satisfactory in the twilight, red will now seem distinctly darker than the blue with which it had been matched.

We have noted the presence of adaptation in discussing many of the receptors, but none approach the eye in range and rapidity of adaptation. Of all, the temperature senses more nearly parallel the eye, although the shift of equilibrium is less in amount and slower in occurrence. What mechanism is to account for this striking shift of threshold? Objective changes that at once suggest themselves are the change of pupillary area, the migration of retinal pigment and the bleaching and reforming of visual purple. Another significant fact is the low adaptive power of the rod-free area of the retina. Let us consider these.

As we have stated, the pupil undergoes a seventeen fold change of area when the brightness of the surroundings is increased one billion times (page 620). It is obvious that, while the prompt response of the pupil may shield the retina from the full force of a sudden light and compensate for slight changes in illumination, it is utterly inadequate to explain the facts of adaptation. We have also seen that if the retinal pigment migrates in man the amount of movement is negligible and, therefore, cannot account for adaptation.

"Duplicity" Theory.—Of the physical changes in the retina the formation and bleaching of visual purple is the only one known to occur in mammals, and various facts, such as the low power of adaptation of the fovea, have already been presented that suggest a connection between the visual purple and adaptation. On this basis an hypothesis was proposed, originally by Schultze, which may now be considered well established by the cumulative effect of evidence of many types in spite of the fact that numerous details are not agreed upon. This is generally known as the "duplicity theory," an unfortunate rendering of the term "Duplizitätstheorie." It assumes a functional as well as a morphological duality of the retinal receptors. The rods are thought to give hueless sensations with a maximal brilliance in the green (the condition found in extreme dark adaptation), poor form perception and great power of adaptation because of the associated visual purple. In contrast, the cones are thought to represent a more specialized form of receptor giving beside brilliance, for which the maximum lies in the yellow, hued sensations, good form perception and moderate power of adaptation.

Normally both rods and cones are involved in each stimulation of the retina; conditions giving approximately isolated responses of either type of receptor may, however, be realized. In the rod-free area cones alone are found; here perception of chroma and form is keenest, and it is assumed that elsewhere the cones have the same capacities. The perception of form clearly involves not only the type of receptor but also the richness of its central connections, so that in a strict sense it cannot be said to be characteristic of either the rods or the cones. The responses of the peripheral retina when the light intensity is below the foveal threshold, and therefore presumably below that of the cones in general, is considered to represent the capacities of the rods at that level of adaptation.

Beside the evidence for regional differences in the retina, the duplicity theory is supported by evidence from comparative anatomy, and from observations on totally color-blind and night-blind individuals. Examinations of the retina of many nocturnal animals (owls) show that the rods are well developed and numerous, whereas cones are so few as to have escaped the earlier workers. On the other hand, in diurnal animals, such as snakes and lizards, the case is reversed and cones are abundant while rods are scarce. Since those animals with a predominance of rods show a preference for the dark and an obviously greater power of adaptation, this strongly supports the above view of the function of the retinal receptors.

There occurs in man a rare congenital visual defect known as total color-blindness, in which no differences of hue are perceived but all colors appear as grays of varying brilliance. The spectrum

thus has exactly the appearance that it presents to the completely dark-adapted eye. If the duplicity theory is correct we might expect the cones to be absent or incapable of their usual function, and for this view there are indeed many indications. The visual acuity is very low and the fovea is in about one-half the cases distinctly defective, presenting a blind spot. Where no such blind spot can be demonstrated the power of fixation is defective and a continual shifting of the gaze or spontaneous nystagmus occurs. Bright light is avoided, not because of discomfort but because vision is poorer than in moderate light. All of these conditions agree with the absence of normally functioning cones and no contradicting feature is observed.

As was noted above, there are individuals in whom the power of adaptation is very slight and who are in consequence night-blind. In good light the fovea appears normal in light sensitivity and hues are normally recognized. Purkinje's phenomenon is absent or less marked. These with certain other features, such as the degeneration of the pigment layer, point to the fact that, although the condition may never represent isolated cone vision there is undoubtedly a very marked abnormality of rod function with practically normal cone vision.

The cumulative effect of these and other observations indicates that the duplicity theory is essentially correct and that the retinal receptors are of two distinct types. The rods give rise to sensations differing in brilliance but not in chroma and, presumably because of their multiple central connections, show poor form-sense. They have astonishing power of adaptation and in twilight vision determine the response of the retina. The cones give sensations differing not only in brilliance but also in hue and saturation and, at least in the fovea where connections are direct, lead to keen perception of form. Their power of adaptation is moderate and in strong lights they determine the visual response.

Local Adaptation.—The phenomenon of adaptation has been discussed in relation to relatively long periods of time and to the entire retina. Marked changes in the physiological state and, therefore, in the sensations from a limited area of the retina may occur. This local adaptation is a prominent feature of vision. If a gray paper of medium brilliance with squares of lighter (white) and darker gray (black) is observed with careful fixation so that the images of its different parts remain on the same retinal areas, it will be found that the contrasts of brilliance become less marked, and if the intensities of the gray squares are not very different, their boundaries not sharp and if all eye movements and winking be sedulously avoided, the entire sheet will finally appear a uniform gray. We may consider that the three grays tend to produce three levels of adaptation in the corresponding retinal areas and that for each of the levels the

light received tends to become an equally potent stimulus, until from the shifts in sensitivity of the retina the brilliance of all parts becomes the same.

If after a period of careful fixation (which need not proceed to the complete leveling out of differences) the gaze is shifted, so that the retinal areas, stimulated by the squares, receive light from the uniform gray ground, a curious appearance rapidly develops. The brilliance of the gray ground to the parts previously stimulated by it appears the same, but to the parts stimulated by the dark gray (black) the gray ground appears much more brilliant (lighter), while to those parts previously stimulated by the light gray (white) it appears less brilliant (darker). A uniform physical stimulus thus produces sensations of three differing brilliances corresponding to the adaptation of the areas concerned, a striking instance of the effect of the retinal state on the sensation.

After-images.—This appearance is known as an *after-image*, but it should be noted that it is the resultant not alone of the previous stimulation but as well of the stimulation under which it is seen. Closing the eyes or passing into a dark room does not mean absence of stimulation, but, on the other hand constitutes a decrease of illumination which, as we have seen is a stimulus, a fact illustrated by the current developed in an eye by the cutting off of the light. The appearance of this type of after-image is dependent on the after-illumination, which may be so chosen that any part of the field will appear lighter or darker than the ground observed. Ordinarily, objects appear to have the opposite relation to their surroundings from that previously observed, as the panes of a window appear as darker areas when the eye is directed to a moderately lighted wall; for this reason they are known as negative after-images.

Such after-images are not commonly noted, since the constant roving movements of the eye prevent the development of any marked degree of local adaptation. Other forms of after-images also require consideration. Some involve hue much as brilliance is involved above; these will be discussed later. Another and complicated series of sensations follow the brief stimulation, particularly of the dark-adapted eye. It will be convenient to discuss these now and in connection with them other temporal relations of the sensation to the stimulus, particularly if this is brief. Certain of the facts apply to chromaticity as well as to brilliance.

Temporal Relations of Sensation.—Although the retina has less inertia than most receptors, neither the beginning nor the end of the sensation correspond exactly with the beginning or the end of the stimulus. The onset of the sensation follows the stimulus after a short lag which varies with the intensity and wave length of the light and the region and state of adaptation of the retina. In Fig. 107 is given a determination of the rise of sensation for three different

intensities of white light, in which the time in seconds is plotted against the just noticeable steps of brilliance of the sensation. It should be noted that this subjective intensity scale has no fractional values. Thus, for the weakest light used (0.057 mc.) no sensation is noticed until the light has been acting for 0.046 second and no further increase in intensity can be detected until it has been acting 0.057 second. The sensation line thus rises with time by a series of steps to a maximum reached at 0.216 second, after which the brilliance declines to the level produced by a constant light which this investigation does not show. It will be noted that the rise of the sensation is the more rapid for the more intense light. Monochromatic lights of different frequencies made photometrically equal (equal in brilliance when seen as constant lights) also show different rates of rise and different times of maximum.

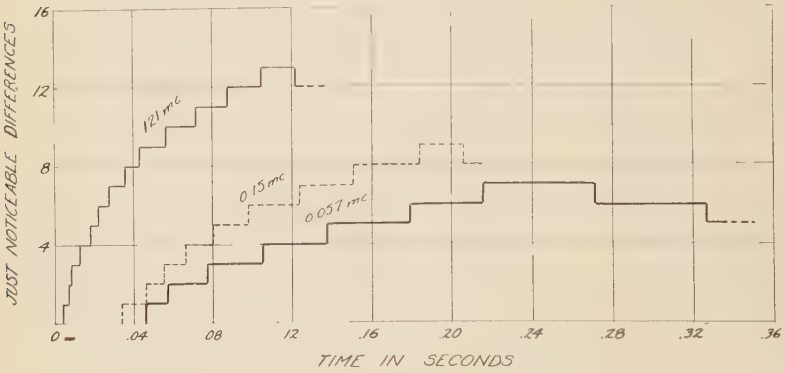

Fig. 107.—Rise of visibility or brilliance.

When light is cut off from the eye, or, to phrase it more correctly, when the eye is stimulated by a decrease in the intensity of light, the history of the sensation is more complex. The results are influenced by the wave length, intensity and duration of the light and by the region and state of adaptation of the retina. With a white light of moderate intensity and short duration and a dark- or partially dark-adapted retina the following variations of sensation are commonly obtained. The *primary sensation* persists for a brief time and is followed by an interval darker than that preceding the stimulation. A *secondary image*, more feeble than the first, follows, and after a second interval of darkness, less intense than the first, there follows a *tertiary image*. The duration varies widely with the conditions, so that no general statement can be given; many of the features occur during the first second and all are completed in perhaps ten seconds. Though much studied, there is not complete agreement concerning these images, the secondary

is said to appear only to the dark-adapted eye and to depend on the response of the rods, but others have held the entire process to be central; with very weak lights all images except the first are said to drop out, with higher intensity to fuse to a continuous sensation.

Fusion.—Both the rise and the decay of the sensation are important for the question of *fusion*, a process involved in the commonest method of "color mixing" and in moving pictures. To illustrate by the simplest example: If a disk half white and half black is revolved while some point, say the center, is fixed, a particular part of the retina receives alternate stimulation of "white" and of "black" (which, as we have seen in the electrical response, constitutes a true stimulus) or, more exactly of increase and decrease of light intensity. With a slow rate we perceive an alternation of black and white; with increased rate the margins of the sections are not clearly seen and the sensation passes into a peculiar oscillatory or tremulous form to which the term *flicker* has been given; with further increase this gives place to a continuous and uniform sensation of gray, in which there is no subjective evidence of the alternating nature of the stimulus; it is then said to be *fused.*

The rate necessary for *fusion* and the *intensity* of the resulting sensation are both matters of interest. It is found that with more intense light a more rapid alternation of stimuli is required; in fact, the logarithm of the intensity is inversely proportional to the time of the individual stimuli.

That fusion occurs is proof of the absence of exact synchronism of stimulus and sensation. It is usually stated to result from the "persistence of vision," that is, from the slow decay of the sensation which links one sensation to the next. Data for the exact analysis of fusion are not at hand, but it seems to rest on both the rise and the decay of the sensation. We have seen that the rise of sensation is more rapid for the more intense stimuli. The decay on cutting off the light, or, better, the stimulus of decreased intensity, is less well known but is apparently the more rapid the greater the decrease of intensity.

With each increase of light the sensation tends to increase in brilliance; with each decrease of light, to decrease in brilliance. If time is allowed for a change in brilliance to occur in either direction *flickering* is noted; if the time is to be reduced below this point it will have to be less, the steeper the slope of rising or falling sensation.

The brilliance resulting from the fusion of two differing stimuli is equal to that produced by a constant light with a brightness equal to the average of the two lights; this relation is known as the Talbot-Plateau law.

Contrast.—Not only does the previous stimulation of a portion of the retina affect its response to a particular physical stimulus, but

the effect of any stimulus is markedly affected by the simultaneous stimulation of other and particularly adjacent parts of the retina. This mutual effect of simultaneous stimuli on the responses evoked is called *contrast.* Contrast affects chroma as well as brilliance; examples are common, and it is a device regularly employed by artists and designers. If a piece of gray paper is placed in succession on a series of gray paper of differing intensities it will be noted that it seems ligher (more brilliant) on the darker backgrounds and darker on the lighter backgrounds. The effect of contrast on brilliance is also shown in Fig. 108. Here those portions of the white

Fig. 108.—Contrast.

strips flanked by black squares appear ligher than those which are opposite white strips, so that at the intersections they seem, particularly when seen peripherally, to be marked by gray smudges.

Discrimination of Brilliance.—The power of brilliance discrimination shown by the eye is of interest not only from the physiological side but because of its practical bearing on photometry or the determination of intensities in illumination. When two areas are compared directly a number of factors influence the keenness of discrimination. These include the size, the nearness and the absolute brightness of the areas and the state of adaptation of the eye.

With ordinary light adaptation and small closely juxtaposed fields, as in a photometer, a difference in brightness of about 2 per cent of the observed intensity can be detected. As for other senses, the fractional part of the intensity that can be discriminated tends to be constant. The range over which Weber's law is applicable is larger in the eye corresponding to its greater range of adaptation. With extremes of light intensity the power of discrimination

falls off, most rapidly at the low intensities. The variations of the ratio of the perceptible difference in intensity to the total intensity at different levels of illumination are shown in Fig. 109.

It will be noted that over an intensity range of 100,000 fold, including moderate and very bright lights (from +3.6 to −1.4 log. ml.), the ratio of perceptible difference varies but two fold and that even the inclusion of extremely feeble lights (down to −4.4 log. ml.) increases the range of the difference threshold only to a little over thirty fold.

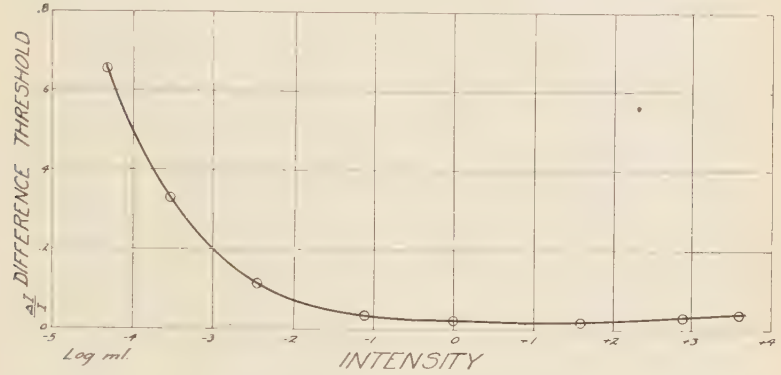

FIG. 109.—Discrimination of brilliance.

The sharp rise in the ratio at the lower intensities is probably related to the rod vision which these conditions favor.

CHROMATICITY.

Dependence of Chromaticity on Nature of the Stimulus.—Although brilliance is an attribute of all colors we have confined our discussion of it chiefly to the *achromatic* series or grays. We will now consider *chromaticity*, that quality of colors which separate the chromatic series from the grays and includes the attributes of *hue* and *saturation* which cannot appear independently and therefore must be discussed to a large extent together. The relation of chromaticity to the physical features of the stimulus will first be considered. The most obvious relation is to frequency or wave length. Radiation containing all frequencies in the proportion shown by ordinary sunlight (see page 591) arouses sensations devoid of chromaticity, and this is also true of certain combinations of properly selected frequencies.

Hue.—All single frequencies and most combinations arouse under ordinary circumstances sensations having hue and saturation. As we pass through the frequencies of the visible spectrum the hue

changes through the "colors of the rainbow." That the traditional hues are seven in number has an historical but little other significance; change in wave length causes change in hue but the power of discriminating hue varies in different parts of the spectrum as shown in Fig. 110. It will be noticed that, in general, discrimination is keenest in the central portion of the spectrum but that there are four maxima of unknown significance. The number of hues that can be distinguished in the spectrum under the most favorable conditions is about 130.

These however do not include all the hues nor are the varying frequencies all the stimuli which produce the given hues. Simul-

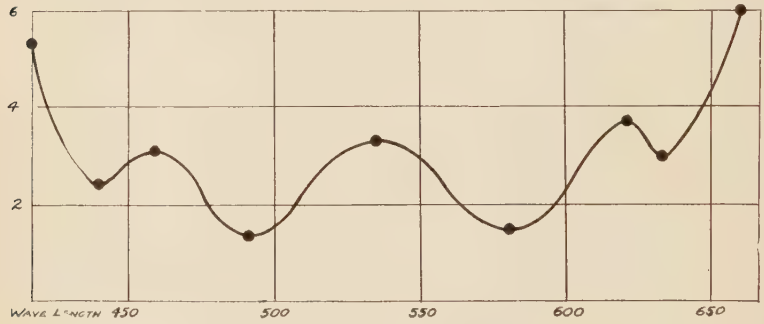

FIG. 110.—Hue sensibility.

taneous stimulation of a part of the retina with light from near the two ends of the spectrum—red and blue—gives rise to hues not in the spectrum (and therefore not producible by any single frequency). These purples comprise some twenty more distinguishable hues bringing the total up to 150. It is also possible, as we shall see later, to duplicate the sensation of certain spectral hues by mixture of other wave lengths, as orange may result from monochromatic light of the proper frequency or from the simultaneous action of two frequencies which separately would appear red and yellow.

The mixture of lights of two frequencies usually gives hues of less than spectral saturation, and certain pairs of frequencies give rise to completely unsaturated or gray sensations. Such pairs are said to be *complementary colors* and are usually set opposite each other in any diagram of the cyclic position of the hues (see Fig. 112).

Saturation.—Saturation is related to the physical nature of the stimulus in the following way. Light of a definite wave length and producing a particular hue will, if mixed with "white" light, that is, light with varied frequencies in the proportion found in sunlight, be seen to undergo a change of saturation. Increasing the proportion of white light will cause the sensation to be less and less satur-

ated until it cannot be distinguished from gray, that is, white, of equal brilliance, a condition that may be called zero saturation.

The degree of saturation of the different spectral hues is not the same. Returning to the diagram of the color solid the position of the spectral hues are not equally distant from the axis; yellow as the least saturated lies nearest to the axis, whereas the violet lies much farther, being the most saturated of the spectral colors.

For any wave length to give sensations of chromaticity it is necessary that the intensity of the radiation and the area stimulated exceed certain minimum values which are greater than those required for sensations of brilliance alone. That the threshold for chromaticity is greater than that for brilliance is easily illustrated. If small pieces of hued paper mounted on a white card are approached from some distance it will be seen that they first appear as darker (less brilliant) spots on the more highly reflecting ground and only later are recognized as hued. With the dark-adapted eye the phenomenon is more marked and a faint light gradually increased in intensity is seen for some time before the hue is distinguished. The interval between the threshold for brilliance and chromaticity is known as the *photochromatic interval* and is longer for the light of high frequencies, being almost absent at the extreme red end of the spectrum.

To return to the color solid as representing the relations of the attributes of color, a number of the lowest levels of brilliance are not accompanied by either hue or saturation and should be represented by an extension of the brilliance axis beyond the solid, a distance equal to the photochromatic interval. It is also true that the lower levels of brilliance which show chromaticity are more restricted in number of hues and steps of saturation, so that the solid should taper toward the end until it is reduced to a bare axis. Apparently also as the upper end of the solid is approached it becomes smaller, since as the glare limit is neared the saturation becomes less and the number of hues fewer.

Relation of Chromaticity to State of Retina.—The hue and saturation aroused by a particular stimulus depend to a surprising degree on the state of the retina. It is not necessary to turn to the abnormal retinæ of color-blind persons for illustrations of the different sensations that a uniform stimulus may produce. The normal retina does not reply with the same sensation to a particular wave length of light falling on its different parts. Such a stimulus moved in from the extreme periphery toward the fovea is "seen," that is, recognized as some degree of brilliance, before the hue is correctly appreciated, and in some cases the first judgment as to hue and saturation differ radically from the final verdict. The threshold for chromaticity is lowest at the fovea and falls off rapidly in all directions; therefore a particular intensity and size of stimulus may, at a certain distance from the fovea, evoke sensations of brilliance

without chromaticity. It is customary to map out with a standard stimulus the zones within which a particular frequency will appear in its correct hue. An instrument for determining the angular extent of such zones is known as a *perimeter* and is used not only in determining the distribution of color perception but also in the detection of certain pathological changes in the eye and the brain. A map of the retinal fields for certain hues is shown in Fig. 111; it

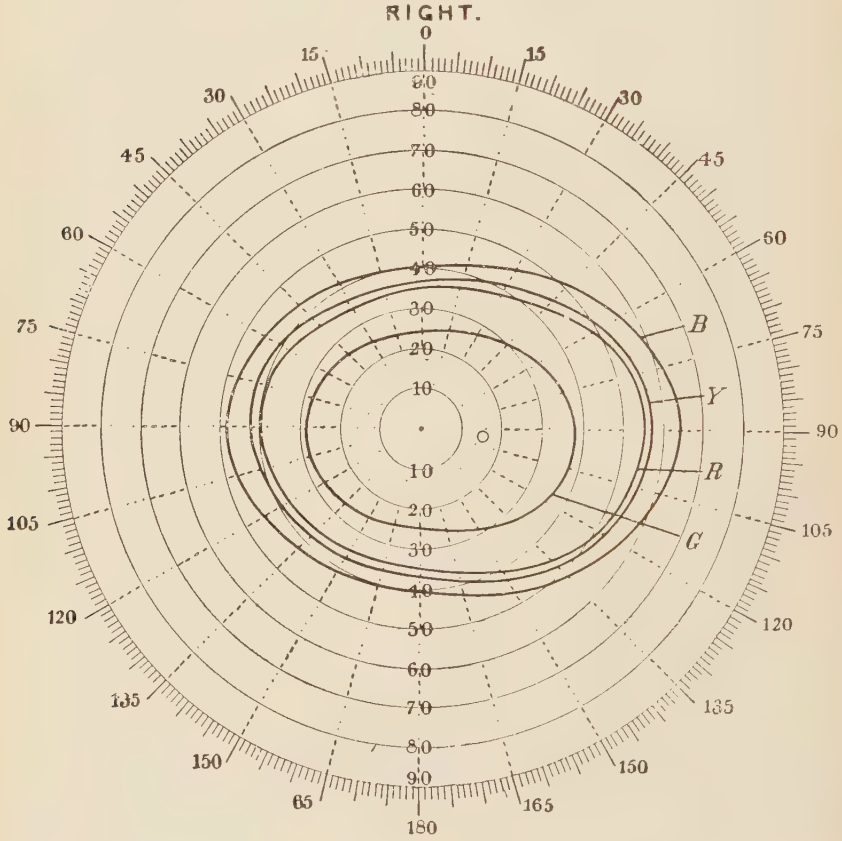

Fig. 111.—Color fields. (Parsons.)

should be remembered that the size of these zones will vary with the size and intensity as well as the particular frequency of the stimulus used, and that outside of a particular zone the retina is not incapable of perceiving that hue but merely has a higher threshold than that represented by the standard stimulus used.

Adaptation.—The effect of adaptation on brilliance has been discussed. The chromaticity of the sensations is also affected, though

in a far less degree. For example, with the relative increase in the brilliance of blue as compared with red in dark adaptation, the blue shows diminished saturation. All parts of the spectrum except the extreme red show some decrease in saturation with dark adaptation.

Local Adaptation.—More conspicuous and interesting are the local alterations of the retinal response following stimulation of a particular portion of the retina which gives rise to after-images (see page 645). If a hued stimulus is carefully fixed so as to confine its effect to one portion of the retina the saturation will be observed to decline and if the original saturation is low and the area small the sensation may entirely lose its hue and become gray.

With a hued primary stimulus and a gray (white) secondary stimulus the secondary sensation will show chromaticity in an often complicated fashion, two phases of which may be mentioned. Under certain conditions the after-image may be *positive,* that is, may show the hue of the primary stimulus for a brief time. More often the after-image is *negative,* showing a hue complementary or approximately complementary to the primary stimulus. A white stimulus, particularly if intense, may be followed by an after-image in which a number of hues appear successively. This effect upon a second sensation of a previous stimulation, known as *temporal* or *successive induction,* is a striking illustration of the influence of the physiological state of the retina upon the sensation, since it is possible by appropriate previous stimulation to cause a series of unvarying physical stimuli ordinarily giving gray, to give sensations of all hues and most of the known degrees of saturation.

Contrast. *Simultaneous contrast* or *spatial induction* results from another form of changed retinal sensitivity. The stimulation of a retinal area induces a change of state in other retinal areas which alters their response. Although generally accepted as retinal in origin it has been claimed by some to be entirely central and certain features, at least, must be of central origin. The contrast effect is most marked in adjacent areas and diminishes with the distance from the point of stimulation, but effects have been observed even in the other eye. As a result, contrast effects are most pronounced with small contiguous areas, even a line separating hued papers reduces the influence of contrast. If the areas are large, contrast is most pronounced at the borders.

Both brilliance and chromaticity are affected by contrast; the former has been discussed (page 647). A gray paper on a hued background gives rise to a sensation having a hue complementary to the inducing ground. Thus a gray paper on a blue ground appears yellow, an effect that is enhanced by viewing the colors through a sheet of tissue paper. A commonly encountered example of contrast is furnished by "colored shadows." If candles are burning on the dinner table while some light still enters through the window, every

object will cast two shadows corresponding to the two sources of light. One of these will be yellow, the other blue. The two sources of light differ in color, the daylight approximating our standard of white, whereas the candle is distinctly yellow. One of the shadows illuminated only by the candle is yellow, that is, gives light of the frequency ordinarily causing a yellow sensation. The table in general is lighted by a mixture of white and yellow, so as to present an unsaturated yellow ground. On this the shadow lighted only by daylight (and therefore usually giving a gray sensation) appears by contrast a distinct blue.

If the paper on the inducing ground is hued, its chromaticity may be altered by contrast. For hues complementary to the ground the saturation will be increased. In some cases the hue is slightly altered.

All the contrast effects, as shown by Allen, may be noted not only by the changes in sensation as described above, but also by the increased critical frequency of fusion, a fact that would apparently invalidate any explanation of contrast based on errors of "judgment."

Color Mixing.—The manifold interesting facts of chromatic vision have attracted many workers and engendered a host of hypotheses intended to bring the facts into simpler relationship. While these hypotheses have led to valuable experimental work they have also given rise to much unprofitable controversy. It is desirable here only to outline two or three of the outstanding hypotheses with relation to those facts of chromatic vision presented above. For an adequate survey of this interesting but complex field some extended treatise, such as Parson's *Introduction to the Study of Color Vision,* should be consulted.

A conception underlying all important hypotheses is that the numerous discriminable sensations, which have been estimated to number many thousands, may arise from fusions of a few fundamental sensations. This view was undoubtedly suggested by the facts of color mixing, which it will therefore be necessary to sketch briefly. At the outset it must be understood that "color mixing," as here used, refers to a very different process from the mixing of pigments in painting and the results are often in seeming disagreement. Instead of mixing the physical bodies reflecting light of varying hues, color mixing is a process presenting two or more stimuli to the same retinal area in such a way as to cause simultaneous excitation by all the frequencies. This may be accomplished by throwing light from two or more spectra on the same part of the retina at the same time or more simply by observing a disk covered with papers of the desired hues while this is rotating at a speed sufficient to give complete fusion.

Extensive experiments in color mixing have shown that all spectral hues as well as the purples may be matched by mixtures of other

frequencies. For certain ranges of the spectrum two properly chosen wave lengths suffice, for others three are required. The results of such experiments may be shown graphically by a *color mixture diagram* or *triangle*, Fig. 112. The exact form will vary somewhat with the units and the wave lengths chosen for fixed points but any such diagram will show a number of important facts. The location of any point within the triangle represents the

FIG. 112.—Color mixture diagram (Troland). The points on the curved lines marked with wave-lengths represent the equivalents of the spectral hues in mixtures of the three hues *R*, *G* and *V* at the apices of the triangle. The percentage of a given hue in the mixture is indicated by the distance from the base opposite the appropriate letter. Thus the red end of the spectrum from 690 to 660 mμ is duplicated by variations in the intensity only of the red mixing hue, from here to 590 mμ by mixtures of red and green, from here to 470 mμ the mixtures include red, green and violet, from here to 430 mμ green and violet, from here to 400 mμ violet only. The extra-spectral purples are formed by mixtures of violet and red. White represents equal per cents of all three hues. Complementary colors will be found at opposite ends of a straight line through "white."

percentage composition in terms of the three fundamental hues by the distances from the sides opposite the angles marked *R*, *G* and *V*. The analyses of the spectral hues in these terms are represented by the points on the line marked with the wave lengths and bearing the names of the chief hues. At either end a number of wave lengths are represented by one point; here a change of wave length is duplicated by a change in intensity only of the one (red or violet)

light. Hues along the straight portions of the triangle may be matched by mixtures of two wave lengths only; this includes the reds, oranges and part of the yellows and the violets and all of the extraspectral purples. Those hues on the curved portions of the figure require all three elementary wave lengths. Mixtures of two spectral hues along the straight portions of the figure will give hues of spectral saturation, along the curved portions will give hues less saturated, as represented by the fact that all points on a straight line joining such hues will lie nearer the central white. Complementary hues lie at opposite ends of a diameter passing through white; that is to say, wave lengths thus indicated when mixed in the proportions in which the diameter is divided by white, will give a completely unsaturated and hueless sensation. As suggested by the diagram it is possible to experience sensations more saturated than those of the spectrum.

The fact that all hues may be evoked by mixtures of three objective stimuli is the basis of color photography and color printing. If one of the small prints in which all of the hues used by the painter are reproduced with surprising fidelity is examined with a hand lens it will be seen that the color consists usually of minute spots of three (or four) hues which when examined by the naked eye "mix" and give the desired hues.

COLOR-BLINDNESS.

While these laws of color mixture apply to most individuals, there are persons for which they are not valid and when the deviation is extreme these are called color-blind. This defect is for the most part congenital and inherited in a definite fashion; although disturbances of color vision due to disease are known they throw little light on the problem of color vision. The most striking form is one in which chromaticity is entirely absent, that is, the sensations may vary in brilliance but not in hue or saturation, and would therefore correspond to the black-white axis of the color solid. Such persons are said to be *totally color-blind* or to have *achromatic* or *monochromatic vision*, although the latter term is best restricted to its physical meaning of homogeneous radiations. This form of color-blindness is rare and is usually associated with other defects of vision, of which the most interesting in the present connection is the low visual acuity often accompanied by a central scotoma or blind spot and the difficulty of proper fixation resulting from this. To such persons the spectrum appears as a hueless or gray band varying in brilliance with a maximum which agrees strikingly with that of the dark adapted normal eye. These and other facts have led a number of authors to regard the defect as one in which the cones are absent or non-functional or in which the neuroepithelium

has the character of rods only. While there are difficulties with this view it is far more satisfactory than any other that has been proposed.

In the other types of color-blindness chromaticity is not lost but is strikingly modified from the normal. We have said that for persons having normal or *trichromatic vision*, all hues can be reproduced by mixtures of three frequencies. Similar experiments with this type of color-blindness have shown that all the hues seen in the spectrum and in addition the purples may be duplicated by mixtures of the two frequencies and hence this type of vision may be called *dichromatic*. Dichromatic vision is found in about 2 to 4 per cent of men and less than 1 per cent of women, following apparently the sex-linked form of inheritance in which the transmission is through the female but in which the defect appears in the male. It is usual to distinguish three forms of color-blindness among the dichromats but for several reasons no attempt will here be made to separate them. While dichromats may be detected by a number of standard tests the subgroups are difficult to distinguish and it seems probable that a three-fold classification will prove inadequate; the division into three types has undoubtedly been influenced by the current color hypotheses.

The color diagram of a dichromat is thus a straight line instead of a triangle, and from two frequencies, one from near either end of the spectrum, all hues may be matched. It follows that for some intermediate frequency, which falls near 500 mμ in the green, white is a satisfactory match, this is called the *neutral point*. For most dichromats the hues which appear red and green to normal vision are imperfectly distinguished or perceived only as differences in brilliance. Since the signal lights universally used on railways and steamships include red and green, this defect assumes great practical importance and tests of color-vision are required of thousands of railway and steamship operatives. Such tests are designed to remove extraneous aids by presenting the hues on bits of yarn or paper and usually include "confusion colors" of gray or brown to furnish a variety of degrees of brilliance in the perception of which the dichromat is not less sensitive than the normal.

COLOR HYPOTHESES.

The general division of function between rods and cones stated in a previous section is accepted by the supporters of most modern theories; according to this view the chromaticity of the sensation depends upon the cones, although brilliance may come from either. The mechanism of adaptation suggested above is also generally adopted.

The first of the important hypotheses and that now numbering

perhaps the most supporters was proposed by Thomas Young in 1801 and nearly fifty years later adopted and modified by Helmholtz, so that it usually bears both names. Following closely the facts of trichromatic color mixtures it postulates three fundamental sensation processes, red, green and blue, from joint excitation of which arise all sensations of hue. The excitation of red, for example, is greatest for a particularly long wave length but is affected in some degree by all parts of the spectrum and so for the other fundamental sensations. White results from the simultaneous excitation of all three in proper proportions. *Contrast* (spatial induction) was explained by Helmholtz as an "illusion of judgment," a view that few are now ready to accept. *Complementary after-images* are looked upon as resulting from the reduction in amount of some substance involved in that sensation chiefly affected by the primary stimulus; subsequent excitation by white light (which should affect all the substances in equal degree) affects the remaining unexhausted substances to a greater extent giving a sensation complementary to the primary sensation. The facts of color mixing make it improbable that the three substances, if they are present, are affected by all parts of the spectrum. The achromatic form of *color-blindness* was supposed to result from the identity of all three color processes, the dichromatic form from the absence of one of the processes. The former defect receives a more satisfactory explanation, as suggested above, by assuming that the cones are non-functional; this in no way weakens the hypothesis. The explanation of dichromatic vision is as satisfactory as any. The less complete color vision of the periphery of the retina is not readily explained by this hypothesis, since the type of vision here found is not that which would result from eliminating one of the processes. The existence of three anatomical structures, as three kinds of cones or three photochemical substances, which might be identified with the three processes, has never been established, but the difficulty of chemical analysis in so minute and unstable a structure as the retina renders such negative evidence of little value. In short this hypothesis is not in conflict with many facts of color sensations and serves to bring a number into more significant relationship; with increase in knowledge, however, various subsidiary hypotheses have been proposed to cover particular cases and the general hypothesis greatly complicated, thus, as in many other cases, the original attractive simplicity has been largely lost.

The hypothesis of Hering, also known as the *opponent colors theory*, was proposed by Hering in 1872. This hypothesis assumes six components. Four of these are the hues *red*, *yellow*, *green* and *blue*, which are considered on psychological grounds to be fundamental sensations of which all other sensations of hue are mixtures. To these are added *white* and *black*, the latter considered as a positive

sensation and not the mere absence of stimulation. These six are arranged in three opposed pairs, white-black, red-green, and yellow-blue, so related that two sensations arise from opposed actions on a single substance. Thus the sensation of white results from the "dissimilation" of the white-black substance, black from its "assimilation." Similarly red and yellow are the result of dissimilation and green and blue of assimilation. *Contrast* is explained by the opponent relation of the pairs. Any process in a particular area excites the opposed change in the adjacent parts of the retina. Thus a yellow stimulus causes dissimilation of the yellow-blue substance which induces an assimilation of the same substance in neighboring areas with a resulting blue sensation. *Complementary after-images* receive a similar explanation, any process induces a rebound in the opposite direction when it is removed so that the complementary hue is perceived. *Color-blindness* of the dichromatic type is assumed to result from the absence of one substance with its two opposed sensations. The forms of dichromaticism found give little support to this view. Total color-blindness would result from the absence of all substances except the white-black. This, like the Young-Helmholtz and other prominent hypotheses, has incited much valuable work but the fact that such discordant views may exist together for many years is conclusive proof that none are satisfactory and that all must in time be displaced or materially modified.

The hypothesis of Ladd-Franklin, called by her the *development theory*, assumes in the rods comprising the periphery of the retina and in the retina of totally color-blind persons a light-sensitive substance giving off under the action of light, a reaction product which is the basis of whiteness. In the cones this substance has undergone a differentiation such that dissociation of portions may occur when acted upon by particular frequencies. In the first step two such groupings are unstable, the dissociation of one by short wave lengths giving sensations of blue, of the other by long wave-length sensations of yellow. This condition is encountered in the midperiphery of the retina and in certain dichromats. In the normal fovea, however, the yellow producing fraction has undergone further differentiation into two portions, one giving rise under the longer wave lengths to red sensations and the other under intermediate wave lengths to green sensations. Simultaneous dissociation of both give rise to the parent yellow, and of all three fractions to the original white sensations. The fully developed retina is thus believed to contain three light-sensitive substances but to give rise to five sensations, red, green, blue, yellow and white. Black is a "non-light sensation," no more closely connected with white than with any other of the colors, and would, therefore, apparently constitute a sixth sensation. Other colors rise from blends of these six.

Complementary after-images arise from the breakdown of the

labile residual portions of partially dissociated molecules. If, for example, a red light acts for a time on the retina it leaves in this part incompletely dissociated molecules deprived of their red-sensation producing portions. The spontaneous breakdown of these leads gradually toward a white sensation and when the light is reduced in intensity or cut off gives rise to a blue-green sensation.

Contrast was first explained on the basis of the unstable remaining portions of the incompletely dissociated molecules just mentioned. Some of these were thought to be swept into neighboring regions by the circulation, and there to give rise to the complementary sensation. For this the retinal circulation is far too slow. Contrast was later said to rest on physiological processes at a higher level than the retina.

As suggested above, color-blindness receives a logical explanation in the development theory. Total color-blindness results from a primitive undifferentiated white substance, dichromatism from absence of either the red-producing or green-producing fraction of the yellow substance.

SPATIAL RELATIONS.

Objects in any part of the visual field may give rise to sensations having brilliance and possibly chromaticity. Such objects may change in regard to the type of radiations reflected or may be replaced by other objects; the sensations will accordingly show temporal relations to such changes, the more important of which have been indicated above. Objects in the visual field will also have spatial relations to other objects and these relations may be changed by movement. These relations will now be considered.

The image of external points on the retina represents the optical projection of the three-dimensional spatial relations of the visual objects on a two-dimensional surface. The retinal points stimulated therefore present in a modified form the positions and movements of external objects. As with other sensory surfaces, such as the skin, there exists some difference in the sensations from the differently placed retinal elements of the same kind which is called *local sign*. It is therefore possible to build up spatial relations between the visual sensations which prove to be of extraordinary delicacy. The topic is complex and in the brief treatment here possible only the salient features will be considered. These will include *extensity*, *direction*, *form*, *motion* and *distance*.

Extensity.—*Extensity* may be looked upon as a prespatial characteristic of visual sensations in that it implies but cannot be analyzed into spatial relations. Two small objects, such as distant lights or periods on the printed page, may be recognized as differing in size without arousing perceptions of different positions for their different parts.

Direction.—Direction is the primary form of perceived spatial relationship as suggested above from the fact that the retina is two-dimensional and receives the projection of objects lying in three-dimensional space. That is, an object is seen as above or below, to the right or to the left of the observer or in a similar relation to some other object. It follows from the principles of image formation that with an immobile or unmoved eye objects occupying a particular position would always stimulate the same part of the retina. With such an unmoved eye the delicacy of the sense of direction that might be built up, would be conditioned by the size of the retinal elements, or rather of the groups of retinal elements represented by a conducting unit. The eye is, however, very mobile; the bearing of this on the perception of direction will be considered presently.

Retinal "Grain."—The term *retinal grain,* which has been used by analogy with a photographic plate, is convenient as designating the physiological capacity for perception of separate images or "resolving power" of the retina. This will depend upon the size of the retinal areas which can be separately stimulated. The immense number of the rods and cones and the nature of their central connection has already been pointed out above; it will be recalled that there exist pathways for about half a million separate receptive units. That so many sensory units can be comprised in an organ as small as the eye giving it the receptive capacity so vividly worded by Paley, "The prospect from Hampstead-hill is compressed into the compass of a sixpence, yet circumstantially represented," is possible only because of the minute size of the rods and cones. The largest of the cones from the peripheral retina has a diameter of about 7.5 μ while the smallest from the fovea measure only one-third of this or 2.5 μ (0.0025 mm.). A statement much more striking is that 30 to 40 such cones laid side by side would be required to reach across the cut edge (thickness) of this page. The rods and cones outnumber the fibers of the optic nerve so far that on the average from 100 to 200 must connect with each fiber. Cajal has given histological evidence that in the fovea this connection is quite direct, approximating one cone for one fiber. This would entail an increased multiplicity of connection at the periphery but this is difficult to determine anatomically.

What are the conditions that would permit the discrimination of adjacent retinal images and therefore of assigning to them different directions? The conditions are clearly the same as those in the skin where it was stated that to discriminate two touches as separate it was necessary that one stimulable but unstimulated element should intervene. In the retina we may assume that between the two stimulated areas there must lie one functional but unstimulated receptive element, which must be interpreted to mean the retinal area supplied by one optic nerve fiber. How does this view and the

anatomical measurement agree with the results of experiments? If a series of parallel lines is used as a test object and the person be required to state the direction of the lines so that the fact of discrimination can be checked, a consistent and reliable measure of visual acuity is obtained. We may conclude that with the smallest lines distinguished, the white lines of the image are wide enough to cover a series (not necessarily continuous) of elements which are therefore stimulated while they are separated by similar rows of unstimulated elements beneath the dark lines. We have said that a separation of 1′ is accepted as average for this test; young adults, however, commonly exceed this standard and acuities of 1.5, or an angular width of line of 40″ are not exceptional. Such an object

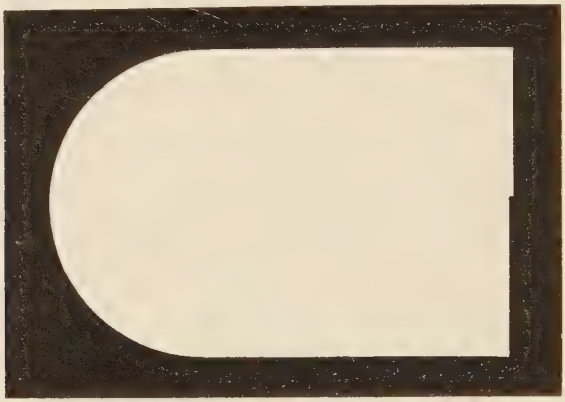

Fig. 113.—Displacement threshold. (Averill and Weymouth.) The offset in the left-hand end of the dark outline is varied in testing. The size here shown will give a retinal image of about 2 μ at 5 meters.

would give a geometrical image with lines 3.3 μ wide. The physical image is less well defined since both aberrations and diffraction reduce the sharp transition from black to white presented by the object. The striking correspondence in width of the lines of the image with the diameter of the foveal cones is convincing proof of the correctness both of the above view of the discrimination and of the "private line" connection of these cones.

Other methods of measuring visual acuity give different results. Thus the *displacement threshold*, the test object for which has the form shown in Fig. 113, may be as low as 1 μ. This value is below that given by histological data for the diameter of the cones. Similar results have led certain writers to postulate some sort of functional subdivision of the cone which would of necessity involve a functional subdivision of the communicating bipolar cell or nerve fiber. These assumptions are so improbable that they do not require

serious consideration. That the subconal discrimination is the result of a sort of averaging process in which a number of retinal elements contribute to the perceived position of each of the dis-

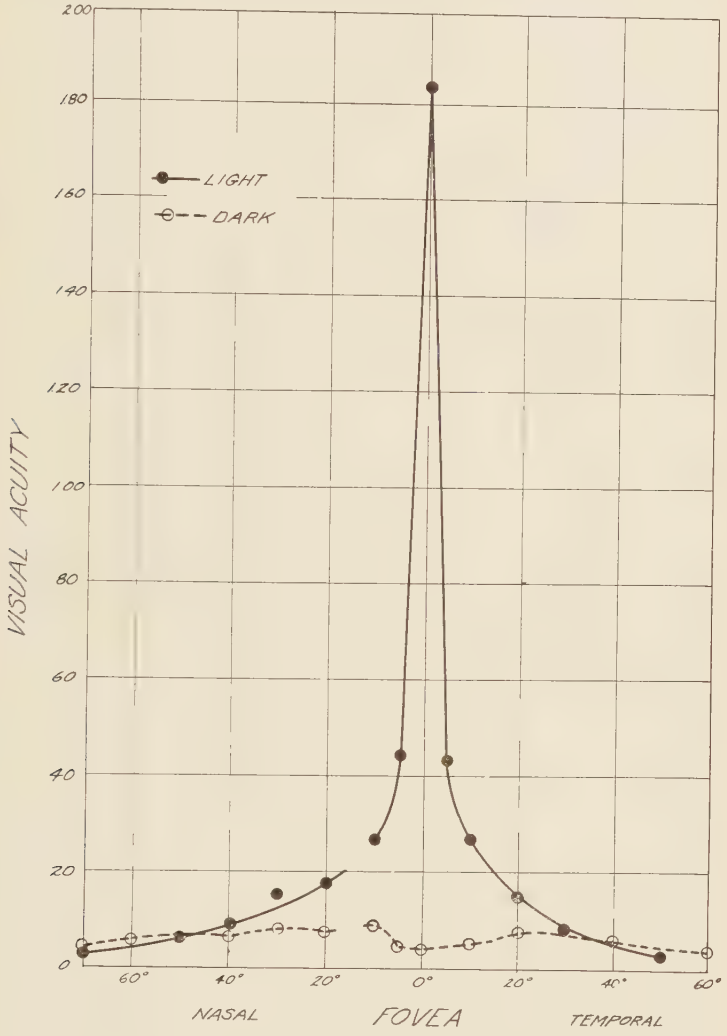

FIG. 114.—Visual acuity of different parts of retina in good and in dim light (Fick). (See text.)

placed segments is indicated by the fact that the reduction in length of these segments rapidly reduces the keenness of discrimination.

To make more graphic the power of discrimination of the retina let us compare it with the most sensitive portion of the outer skin—

the finger tips. Here the separation of the compass points that can be recognized is approximately 1 mm. If we assume 3 μ for the fovea, which is a conservative figure, this is less than 1/300 of the separation required for touch. If we further assume that the retinal area for which this high sensitivity holds is 0.5 mm. in diameter, it would follow that for the finger tip to contain as many sensitive areas it would have to measure 300 x 0.5 mm., or 150 mm., in diameter.

Regional Differences in Visual Acuity.—The retina, however, does not show this high sensitivity over its entire extent. From this level which is found at the center of the fovea the acuity falls off rapidly as we pass in any direction toward the periphery until at 60° it is less than 1/30 of its central value. Yet even here the retina is more than five times as sensitive as the finger tip. A graph of the regional visual acuity as determined by Fick is given in Fig. 114. It will be noted that the decrease of acuity is more rapid on the temporal than on the nasal side. The dotted line represents the acuity for dim illumination and therefore partial dark adaptation. Under these conditions the fovea is less sensitive, as has also been pointed out for the light threshold (see Fig. 104).

Although there exists no sharp transition it is customary to speak of *central* and *peripheral vision*. It is of course not possible to determine the regional variation of visual acuity in animals, but from the histological evidence and the data of animal behavior it seems probable that although in most mammals the central portion of the retina may be more sensitive to form than the periphery, central vision comparable to that of man is restricted to forms having a fovea, that is, the higher primates and many birds. For the admittedly superior vision of these animals the fovea with its higher acuity is a prime necessity.

EYE MOVEMENTS.

From a consideration of retinal grain and visual acuity we will now pass to the question of eye movements and their relation to the regional variations of acuity, which will complete the data necessary for understanding the mechanism of direction-perception.

It has been stated that if the eye were immobile an object in a particular position would always stimulate the same part of the retina. But the eye is mobile and almost constantly in motion. With a constantly changing relation between the retinal field and external space, how is it possible to build up spatial relations between visual sensations and between them and other sensations?

In order to discuss this important question intelligently it is necessary to consider the ocular motions themselves. The situation of the eye and the disposition of the ocular muscles have been

briefly outlined in Chapter XXXV (see page 582). The bulb lying in the orbital fat, a relation almost exactly that of a ball-and-socket joint, has a considerable degree of freedom of rotation about any axis. Movements may be analyzed into terms of three reference axes in accordance with the following definitions:

When we "look" at an object, the eye is said to *fix* the object, although, as we shall see, it might be more proper, as Maddox suggests, to say that the object fixes the eye. That is, the eye takes such a position that the image falls on the most sensitive portion of the retina, the center of the fovea. The *line of fixation* is a line passing through the point fixed and the center of rotation under these conditions, or less exactly but without serious error the point fixed and the fovea. The antero-posterior axis determined by the line of fixation is then the first of the three axes of rotation; rotation about this will be called "rolling" (the term used by Helmholtz was "Raddrehung"). The *primary position* of the eyes is that in which, with head erect, the eyes are directed to a point on the horizon; the lines of fixation are then parallel. The second axis of rotation is a horizontal line passing through the centers of rotation of both eyes when they are in the primary position; rotation about this constitutes "elevation" or "depression." The third axis is a vertical line perpendicular to the first and second axes through the center of rotation of each eye; about this axis occurs *right* and *left rotation*.

Physical limitations to rotation are imposed by the check ligaments, special thickenings of the fascia bulbi, and by the attached conjunctiva; these rather than the capacity of the muscles apparently set limits to the various rotations. By no means are all the physically possible movements, however, actually carried out, the physiological movements being limited in accordance with certain features of the normal use of the eyes. These physiological limitations are in part monocular and in part binocular, that is, concern the simultaneous movements that may be carried out by the two eyes; these will be considered later.

Field of Fixation.—All the external points that may be fixed by movements of the eye while the head is stationary constitute the *field of fixation* which must not be confused with the visual field or with the fields for certain hues determined with both head and eye stationary. The field of fixation thus measures the capacity for rotation about the horizontal and vertical axes although in some details the limits of the field are set by the interference of the nose and brow. The horizontal and vertical extents of the field are approximately equal, measuring about 100°, which is equally divided between right and left rotation but in the vertical, movement is greater down (60°) than up (40°).

Rotation about the antero-posterior axis (rolling) is extremely limited as compared with that about the other axes and much less

than we would expect to be physically possible. Rolling cannot be carried out voluntarily and is of course unnecessary for fixation. In animals with laterally directed eyes, such as the rabbit, rolling is reflexly induced by the labyrinth when the head is tilted nose up or down. In other words, when the retina would suffer a rotation about the antero-posterior axis with regard to external objects because of the movement of the head, there occurs a reflex compensatory rotation in the opposite direction and the horizontal meridian of the retina (determined by the intersection of a horizontal plane through the center of rotation when the eye is in the primary position) remains horizontal. Much smaller reflex rotations never exceeding 20° and seldom equalling 10°, and compensating for but a fraction ($\frac{1}{3}$) of the displacement of the eye, occur in man when the head is tipped down on the shoulder. This lessened capacity for rolling in man is apparently associated with the forward directed optic axes involved in binocular vision, since the head is less often turned so as to cause a relative rolling of the retina with external objects. Certain other features of rolling will be considered later.

Action of Individual Muscles.—With these features of the eye movements in mind and recalling the disposition of the muscles previously given (see page 582) the action of the individual muscles may be considered. The effects produced by their contractions will be briefly outlined for the primary position only, that is, the position in which the eyes are directed forward to a distant horizon while the head is erect. It must be remembered that the effects will vary for each position of the eyes. The six muscles may be grouped in three approximately antagonistic pairs, each with a common axis of rotation. The simplest effects are those produced by the medial and lateral recti which cause rotation about a vertical axis practically identical with the vertical reference axis defined above. When these muscles contract the line of fixation moves in a horizontal plane medially (nasally) for the medial rectus and laterally (temporally) for the lateral rectus. The movements of the line of fixation are representated by the horizontal lines marked *m.r.* and *l.r.* in Fig. 115.

The superior and inferior recti cause rotation about an horizontal axis which, however, is not the same as the horizontal reference axis joining the centers of rotation. It is approximately perpendicular to the axis of the orbit and thus the nasal end lies about 27° in front of the reference axis. The contraction of the superior rectus will, therefore, cause the line of fixation to be elevated but also to move inward (nasally) and to rotate (roll) so that the upper end of the vertical meridian tilts inward. This is represented in Fig. 115, by the point marked *s.r.*: the short line indicates the resulting position of the vertical axis.

The direction of action of the superior and inferior obliques differs from that of the recti since the origin of the inferior and the

pulley of the superior cause them to pull forward and nasally; the axis of rotation thus has its nasal end directed backward toward the apex of the orbit making an angle of about 51° with the line joining the centers of rotation. A contraction of the superior oblique

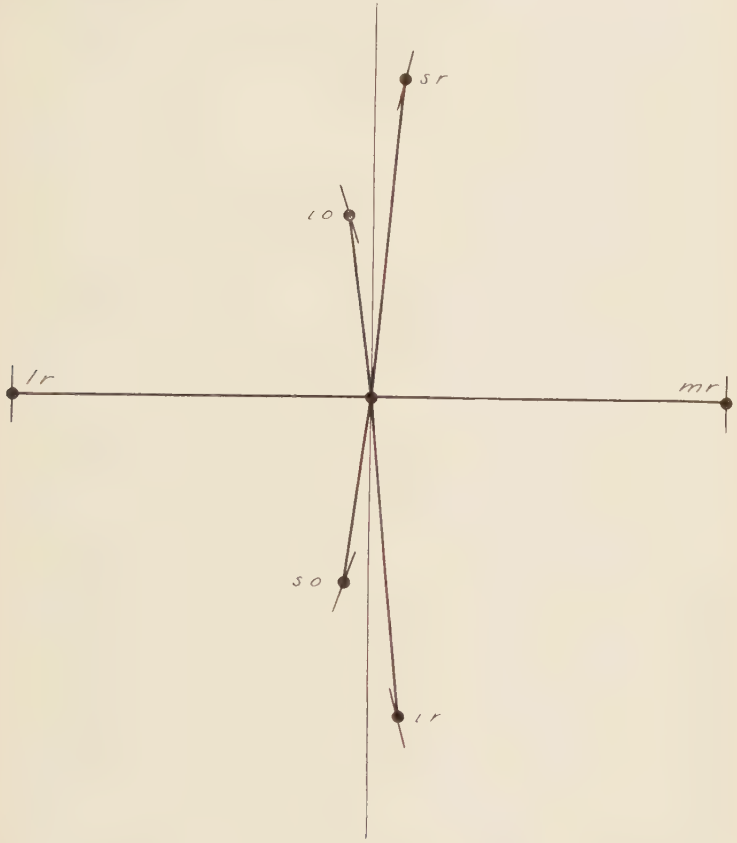

FIG. 115.—Action of individual eye muscles (Hering). The central point represents the position of the cornea (or line of fixation) in the primary position; the six points at the extremities of the lines the positions after equal rotations about their axes by various muscles; the short lines through these points represent the positions of the vertical meridian of the retina in that position. *lr*, lateral rectus; *io*, inferior oblique; *sr*, superior rectus; *mr*, medial rectus; *ir*, inferior rectus; *so*, superior oblique.

will therefore cause the line of fixation to be depressed and to move outward (temporally) and to rotate so that the upper end of the vertical meridian tilts inward. This is represented by the point *s.o.* in Figure 115. Since the axis of the obliques most nearly approaches the antero-posterior axis of the bulb, their contraction causes more rolling and less elevation than that of the superior and inferior recti.

Such are the approximate actions of the individual muscles starting from the primary position; it will be clear that as the eye departs from this position all actions must progressively change. But while an accurate knowledge of these actions is necessary for the ophthalmologist who wishes to analyze the result of an injury to an individual muscle, we must not lose sight of the fact that *all* of the muscles participate in *every* movement of the eyes, and the integration is not muscular but nervous. It is an important fact for all muscular activity that not muscles but *movements* are the entities that appear in our consciousness and in our activities and that these movements are the result of what may be called a *muscle pattern*, that is, a grouping of coördinated muscular activities, the organization of which is to be sought in the central nervous system. It will not be possible to give here more than an example of such a pattern from the eye with part of the proof of its cortical localization.

The muscles taking part in a movement may be classified as (*a*) *prime movers*, (*b*) *synergists*, (*c*) *fixation muscles* and (*d*) *antagonists*. The prime movers are chiefly responsible for the movement; the synergists aid in a minor degree, often only taking part in a particularly extensive or vigorous movement; the fixation muscles prevent movements not intended, as when the wrist is immobilized during flexion of the fingers; the antagonists are muscles, the contraction of which would have the opposite effect from that of the prime movers, their participation consists of a regulated relaxation. A particularly interesting example has recently been given by Maxwell. The stimulation of the right horizontal semicircular canal in the shark causes the right eye to sweep forward and the left eye backward corresponding to a left rotation of both in man. If the muscles are separated from the right bulb and their contractions recorded separately it is found that the internal rectus contracts strongly (prime mover), the external rectus relaxes (antagonist), while the other four muscles contract slightly (fixation muscles). Because of the situation of the eye the steadying effect of the fixation muscles is particularly important for the carrying out of delicate movements. The relation of antagonists is not an invariable one; in the present case the superior and inferior recti contract simultaneously as fixation muscles, but for elevation or depression of the eyes they are antagonists. The antagonistic relation is not inherent in the muscles or the peripheral nerves but is a feature of the participation of the muscles in a particular pattern, a fact obscured by the emphasis that has been placed on reciprocal innervation.

That the seat of the pattern is cortical is indicated by two lines of observation. Local cortical stimulation is known to produce many movements but not isolated contractions of muscles; in the monkey, movements of both eyes up, to the right and other combi-

nations have been obtained by cortical stimulation. Apparently these same centers exist in man as "paralysis" of movements to the right, for example, may occur although the individual muscles and their nerves are normal as is shown by their participation in other movements.

From this it is clear that eye movements, both monocular and binocular, depend upon nervous organization, chiefly at cortical levels. The distinction between physically and physiologically possible movements is, on this basis, understandable.

Types of Eye Movements.—The monocular movements carried out within the field of fixation discussed above are of various types of which at least two require separate consideration. It will be noted that both are related to fixation.

If we give attention to an object in not too rapid motion we may maintain a quite accurate fixation by movements of the same angular velocity as the object. These are called by Dodge *pursuit movements*, and occur for example in watching the face of a person passing in a moving train or fixating a point on the swinging pendulum of a clock. Objects thus followed are clearly seen since there is practically no relative movement between image and retina.

Fixation is ordinarily shifted from point to point by rapid *saccadic movements*. This common type presents a curious mixture of the characteristics usually contrasted as voluntary and reflex. The normal stimulus is an object of increased conspicuousness, whether from sudden increase in brilliance, change of hue or motion; such an object "attracts attention" and is usually fixated by an involuntary saccadic movement. The involuntary nature of such fixation is well shown by the extreme difficulty of maintaining fixation in the face of movements in other parts of the field or even more clearly by the following illusion. If two points of light not widely separated in an otherwise totally dark room are alternately exposed and covered, each as it appears will be fixated and in so doing its image will be swept from a slightly excentric position to the center of the retina. So completely unconscious is the movement of the eye that nearly everyone will attribute the movement to the lights and "see" a single point of light moving to and fro. The saccadic movements are rapid, 20° being covered in about 0.05 second and 40° in 0.10 second. This rate, moreover, cannot voluntarily be altered. The slow movements which everyone confidently attempts are found to consist of a series of short movements with intermediate fixation points; actual regulation of rate appears to be possible only by regulating the movement of the fixation point, that is, by the pursuit type of movement.

While under certain conditions fixation occurs involuntarily and at a rate which we cannot control, we feel that fixation is voluntary and this is true in a certain sense because we can fix any object that

we choose in the visual field. The reaction time (0.16 to 0.19 second) is also that of a voluntary movement such as pressing a key in response to a visual stimulus and about three times that consumed by an undoubted reflex such as winking.

During saccadic movements there is normally no clear perception either of the objects passed over or of the movement. Whether this is due to the greater rapidity of this type of movement which does not allow time for normal stimulation or, as claimed by some, to a momentary central anesthesia is not satisfactorily established.

Fixation and the Sensory Gradient.—Fixation movements are related in an intimate fashion to the sensory gradient which the retina presents in a higher degree than any other receptor. A conspicuous object provokes a movement, which shifts its image from a point of low to one of high or rather the point of highest sensitivity. Voluntary movements are only possible in the sense that we can select the object the image of which is to be moved up the gradient. Great difficulty is found in moving the eyes in a normal manner when looking at a uniform surface or in the dark, that is, in the absence of clear images which may be shifted up the gradient. We cannot reverse the process and shift an object fixated to some peripheral region of the retina, that is, down the gradient to a point of low sensitivity, except indirectly by selecting a new fixation point in such a position that the previous one will be shifted in the desired direction, a quite unusual act.

Prolonged exact fixation is not normally required but may be maintained; the conditions are instructive. In the dark or in the absence of a distinct fixation point or when the attention is not directed to any feature of the visual field, as in a "brown study," the eye is in almost constant motion. A plain or vaguely figured surface, such as cloud, cannot be fixated steadily, the eye gropes until a satisfyingly sharp image is found. Both a clear image and a distinct sensory gradient seem to be necessary for accurate fixation. Thus when the "peak" of the gradient is absent, as in cases of central scotoma, fixation is extremely uncertain. An unusual situation is presented by the dark-adapted eye in which, as we have seen, the fovea is no longer the apex of the gradient but relatively a blind spot. The imperfect fixation then carried out is paracentral, a more sensitive region several degrees distant taking the place of the fovea.

With attentive observation saccadic movements of some extent are found to be corrected at the end by slight additional or reverse movements and very minute shifts of fixation can be made. It has been stated that the smallest possible voluntary movement approaches the ordinary spatial discrimination of the retina, that is, one degree, but this is apparently too small. Movements of this size have been calculated to involve the activity of a single nerve

fiber and the muscle fibers which it supplies; if this were true the eye movements would utilize the ultimate physiological capacity of the neuromuscular apparatus.

That vision is the dominant sense in the behavior of birds and primates is undisputed; what advantages does the distinct retinal gradient, of which the fovea represents the morphological culmination, confer on the vision of these forms in which it reaches its highest development? Would not a retina all of the high sensitivity of the fovea be more advantageous? We can confidently assert that, on the contrary, it would be a handicap. A uniformly high sensitivity would require an immensely greater number of final conducting neurons for the optic nerve or a much smaller extent of retina with a reduced field, neither of which would be advantageous. Optically satisfactory images would not be possible at great distances from the optic axis, with a marked gradient these imperfections are of no consequence. It is possible to present more objects in a visual field that can be grasped by the attention, a further multiplication of detail would bring confusion and not benefit. These are, however, minor features; the real significance of the gradient is for spatial perception since upon it rests directed eye movements with perception of direction and binocular vision with perception of distance.

In the directive influence of peripheral stimulation on fixation movements we have the basis of the visual perception of direction. Each peripheral point of the retina carries a sign of the ocular movement necessary to fix it. Even though this movement is not executed its extent and nature is recognized and the proper direction can be assigned to the object; for example, a finger may be placed upon it without fixating it. As a result retinal stimuli are localized in terms of what might be called a system of polar coördinates with the fovea as its center, thus establishing *direction* with reference to the fovea. With uniform sensitivity fixation and this reference point would be lacking.

Listing's Law.—*Absence of Rolling Movements.*—It is clear that with such a system unregulated rolling or rotation about the line of fixation would bring hopeless confusion. We have seen that movements of the head which would alter the relation of the horizontal meridian of the retina to the horizon are compensated by reflex rolling. It is also true that when the fixation is shifted from the primary position to a secondary position up, down, right, left or in any oblique direction no rolling occurs, a result not insured by the physical relations of the muscles. That the eye movements obey *Listing's law*, as this type of movement is called, is an important fact for the perception of direction. Apparent deviations occur in oblique positions as the result of projecting an external plane upon a non-parallel retina and slight actual departures in convergence.

Perception of the Position of the Eye.—We have seen that retinal stimulation is localized with reference to the fovea, but this is not a fixed point and therefore the localization is not complete. When different objects are fixated the eye assumes different positions in the orbit and these positions are recognized through the proprioceptors in the eye muscles. But the orbit is not fixed in position, if the head is moved, the same position on the orbit is related to a different place in the external world. The position of the head is perceived through the muscles of the neck and the labyrinths. On this compound basis the direction of the line of fixation is related to other percipient parts of the body as the finger-tips.

We have thus a two-fold basis for spatial perception, first a sensory field so graded in sensitivity that all stimuli are related to its center, and second a delicate directive apparatus by which this field may be turned in various directions and from which arise muscular sensations relating its position to that of the rest of the body. These retinal and proprioceptive sensations fuse intimately giving a perception of direction in which the relative importance of the two elements cannot easily be estimated. This intimate fusion is to be expected since stimulation of the retinal gradient tends to produce movement and all movement except long excursions of the saccadic type cause a successive stimulation of a series of retinal points over which the image is shifted. The relation is exactly that between the skin and the muscle sense of the arm in which the external object is perceived by the skin but the spatial relation of stimuli on different parts of the skin arise primarily from proprioceptive perception of motion.

"Inversion" of the Retinal Image.—The skin and the retina, however, differ in two essential respects. In the first place the skin may be perceived through other senses—the skin of the hand by the skin of the other hand or by the eye—whereas the retina is completely inaccessible to other senses. In the second place objects stimulating the skin act directly upon it and are in contact with it, whereas the objects known by sight act upon the retina through the intervention of light. It thus occurs that when the left side of the palm is stimulated the stimulating object is found by all the other senses to occupy the same position as the affected skin, that is, the left side of the palm, whereas because of the laws of image formation, a stimulation of the left side of the retina is found to result from an object on the right, or the lower part from an object above. Since the retinal image can never affect any receptor except the retina the knowledge of this relation came only with study of the anatomy of the eye and of optics. To persons ignorant of the nature of spatial perception and impressed by the apparentlly paradoxical physical situation thus revealed, this created the imaginary problem of the "inversion" or "reinversion" of the retinal image. That

the retinal image is inverted with respect to external objects is an elementary fact of physics; that the habitual stimulation of a certain point of a sensory surface by objects having a certain external position, whatever the nature of this constant relation, should lead to the correct localization of a stimulation of this part of the retina is an equally elementary fact of the genesis of localization in all receptors and cannot be looked upon as a special problem in the case of the eye. Examples of redevelopment of correct localization after alteration of the customary relations are numerous; it is sufficient to cite the experiment of Stratton in which after wearing a set of lenses by which an "erect" image was produced there developed out of the resulting confusion an agreement between the retina and the hand as to the position of external objects.

To summarize, we possess in the retina and the motor apparatus of the eye a mechanism for localizing visual objects in terms of *direction*, or to use a common but less appropriate expression, the stimulation of any retinal point is *projected* to the appropriate external point. The fineness of discrimination of direction under favorable conditions may equal 1′; for the comparison of horizontal distance of 15° or 20° the accuracy is from 1/80 to 1/100 of the distances compared.

FORM.

The perception of form as involved in the recognition of geometrical bodies or letters clearly rests upon the power of discrimination of the retina and the perception of direction. The form of a body represents a complex percept not readily amenable to physiological analysis; thus in reading, words or groups of words are perceived rather than the individual letters in the case of familiar material but not in a strange language, even the novel position of the familiar forms as in the inverted page of a book makes recognition very difficult.

MOTION.

The perception of motion is obviously closely related to that of direction; an object perceptibly changing its position is perceived as in motion. There is, however, evidence that motion may be perceived as such, as in the extreme periphery of the eye where a movement may be detected, although the positions involved cannot be correctly discriminated. Apparently it is one of the earliest forms of visual perception. The detection of motion, like visual acuity, is keenest in the fovea but its peripheral decline is not as rapid, so that it is relatively, but not absolutely, better in the "tail of the eye." It may be perceived as the result of successive stimuli of retinal elements as with a moving image on a stationary retina, or from the proprioceptors of the eye muscles when in a pursuit movement the image does not move with respect to the retina.

DISTANCE.

Localization is complete when to the direction perceived monocularly in a roughly hemispherical shell is added distance. Visual perception of distance is chiefly binocular yet there are important monocular clues which must first be considered.

Monocular Clues of Distance.—For the single stationary eye distance is judged from clues many of which are well illustrated by the usage of artists.

Apparent Size of Objects.—The apparent size of familiar objects is one of the most common of these clues. For example, the images of men in a landscape may differ in size by as much as a thousand fold yet this is not thought of as a difference in size but as a difference in distance. Of the same nature is the linear perspective of a series of similar objects such as fence posts or telegraph poles, and the convergence of road margins or railroad rails is one of the commonest devices of the artist to simulate distance.

Aerial Perspective.—We are accustomed to see distant objects, such as mountains, less distinctly because of the haze in the intervening air. In accordance with this fact the artist paints the objects in the foreground with greater clearness than distant hills. An interesting illusion results when a distant peak is seen through the clear smoke-free mountain air, appearing but an hour's walk away, although we may know it to be forty miles distant.

Shadows and Intervention.—The relations of shadows and intervention or partial covering of a distant object by a nearer are also signs of distance.

All these are possible for the single eye at rest and may therefore be used in painting or drawing in which but two dimensions are involved as in the retina. Two other signs of distance are possible to the single eye but involve activity; accommodation and parallax.

Accommodation.—The effort involved in focussing the eye for different distances and the associated fact that two objects at different distances are not seen with equal clearness at the same time, give a basis for the judgment of distance. The slight change necessary to shift from five or six meters to infinitely distant objects restricts the significance of *accommodation* to relatively near objects. Normally this clue is combined with that of convergence, a binocular function soon to be considered.

Monocular Parallax.—If the head is moved sidways objects appear displaced by an amount inversely proportional to their distance, the near ones moving markedly and distant ones imperceptibly. As a result, if the head is moved from side to side while observing a number of objects these will show differential displacement and it will be possible to assign to them their relative distances quite accurately. This habit of observation is soon acquired by persons

who have lost one eye or in cases where only one eye can be used as with a hand lens. *Differential displacement* or *parallax* is the most accurate of the monocular clues.

BINOCULAR VISION.

The most delicate perception of distance, however, depends upon the simultaneous use of the two eyes in binocular vision. Binocular vision as found in man represents a complex and certainly secondary use of the eyes but its possible evolution is too uncertain to detain us here. It involves simultaneous perception of the same object by both eyes and therefore that the eyes have at least some part of the visual field in common. Certainly in its highest form it requires the simultaneous fixation of a single object by both eyes; binocular vision comparable to that of man is impossible in such animals as the rabbit in which the optic axes diverge by practically 180°, and extremely doubtful in some forms in which the visual fields clearly overlap anteriorly.

In man the fields of fixation of the two eyes overlap to a large extent giving a *field of binocular fixation* not much smaller than the monocular fields.

Binocular Movements. The function of binocular movements is to give binocular fixation within this common field, simultaneous fixation, therefore, necessitates certain habitual relations between the position of the two eyes. For objects at a considerable distance the lines of fixation must be kept parallel in all positions. Such movements in which parallelism is maintained are called *conjugate movements*. Conjugate movements have a deep-seated nervous basis; they appear very soon after birth and persist for years after one eye has become blind and is therefore incapable of fixation itself.

It is only in the fixation of near objects that the lines of fixation must depart from parallelism in convergence; this type of movement may be called, in contrast to the above, *disjunctive*. In both types of movement rolling does not occur and the horizontal meridians of the two eyes remain parallel. Both conjugate and disjunctive movements may be classed as *directive movements*, since they serve to direct the gaze to all parts of the binocular field.

The nervous mechanism underlying the directive movements insure that the two eyes are directed approximately but not exactly at the same point. Thus, if one eye is covered by a card and the other fixed on an object in the binocular field and the card quickly withdrawn the object will usually be seen double and then fuse showing that the approximate position had been assumed by the covered eye and that this had been adjusted by an additional fixation movement. Such *adjustive movements* are an important feature of binocular vision. If unusual conditions are presented these

adjustive movements for this final adjustment may involve in slight degree movements never otherwise executed. Thus, if a small prism is placed with the base up or down before one eye exact binocular fixation is only possible by directing one line of fixation above that of the other (*sursumvergence*) a disjunctive movement physically possible but never normally made. Similarly a slight actual *divergence* or a slight rolling may be induced.

Not only are the extraocular muscles linked in these binocular movements but with convergence is associated accommodation and constriction of the pupil. All of these activities may be considered conditioned reflexes linked together in consequence of their normal association in the act of vision. At all times the positions of the eyes and the degree of accommodation are such as approximately to fit the eyes for vision under the particular conditions; a final and extremely delicate adjustment is effected by the reflex-like tendencies to fixate and to focus.

Relations Between the Two Retinæ.—Ordinarily an object gives rise to two retinal images which are perceived as one. Although the perception of one object from two stimuli is a conspicuous and highly developed feature of vision it is by no means unique but occurs with other receptors. We hear a single sounding body with two ears and feel a single pencil with several fingers of one hand or even fingers of both hands or with two lips if we press it against them.

Yet we know that a single object is at times "seen double." What are the conditions for single and for double binocular vision? The retinal relations involved may be stated in the following definitions: *Corresponding points* (or *identical points*) are pairs of points, one on each retina, the simultaneous similar stimulation of which gives rise to single perception. *Non-corresponding points* (or *disparate points*) are similarly those which give rise to double perception or *diplopia*. These definitions will be clearer from further discussion.

Images producing sensations of the same size, form, chromaticity and the like and referred to the same direction in the outer world, are by a natural further step referred to the same object, an unconscious judgment often verified by touching the object. We have seen that fixation brings both eyes so to bear on the object of attention that its image falls in each fovea. The direction of a point fixated is known with great accuracy from the motoceptors of the external eye muscles. Under normal conditions, therefore, the similar images in the two foveæ are correctly referred to one object. So strong is this tendency that similar images made to fall in the two foveæ are unhesitatingly ascribed to a single object; thus, if two holes separated by the interpupillary distance are pricked in a sheet of paper and held before the eyes; the two pinholes appear as one in spite of our knowledge to the contrary. With foveal images it is difficult or impossible to distinguish the three possibilities, namely, the stimulation of the right fovea, the stimulation of the

left fovea or the stimulation of both; the observer is forced to experiment with closing first one eye and then the other. The foveæ are thus the corresponding points *par excellence.*

In the same way objects in the neighborhood of that fixated produce images upon symmetrical parts of the two retinæ and are correctly referred to similar objects having the same direction and therefore identical. The anatomical relation of these points is such that superposition of the two retinæ without rolling and with coincident lines of fixation would superpose corresponding points. It must be remembered, however, that the definition of corresponding points is physiological and not geometrical and that many corresponding points are not superposable.

We have seen that fixation insures that the foveæ receive images of the same object. It is also true that the simultaneous similar stimulation of approximately corresponding points in other parts of the retina causes the eyes to be so directed that the images fall upon corresponding points: this is called the *fusion tendency.* The adjustment resulting from fixation and fusion is surprisingly accurate.

Binocular Perception of Distance. –Similar images on corresponding points give single vision, on widely disparate points double vision or *diplopia.* The condition commonly causing disparate stimulation is difference in the distance of the objects observed. If we look at a distant tree or a spot on the wall and hold a pencil before the eyes the pencil will be seen double, or if we turn our attention to the pencil the distant objects will be doubled. The geometric necessity for this is apparent from Fig. 116. Here the two eyes are fixated upon the point F, the two images of which fall in the two foveæ (corresponding points F in the projections of the retinæ below). A second point F′ near F will stimulate corresponding points on the left of each fovea (F′ below). The images of a nearer object N will fall in different directions from the foveæ in the two eyes, to the left in the left and to the right in the right (noncorresponding squares N below). The image seen with the left eye will, therefore, seem to lie to the right of the object fixated and that with the right eye to the left; this is known as physiological *crossed* (or *heteronymous*) *diplopia.* Similarly an object more distant than F would also stimulate disparate points, in this case lying nearer together than the foveæ; therefore, the image seen by the right eye would seem to be on the right, and that seen by the left on the left; physiological *uncrossed* (or *homonymous*) *diplopia.*

It is clear that only those points in certain geometric relations to the fixation point, that is, in the *horopter,*[1] can actually be imaged

[1] The horopter, containing all the external points which will be imaged on identical points of the retinæ, presents a complex geometric form dependent upon the position of the fixation point, of the head, of the eyes and other factors and would require more space for its consideration than is here available; it would include those points at the same distance and not far to the right or left of the fixation point.

on retinal points equidistant from the fovea. If the term *identical points* is reserved for this relation, it is obvious that images may fail to stimulate identical points and still stimulate corresponding points, since objects somewhat nearer or farther than that fixed are seen as single. We might then visualize corresponding points as circular areas surrounding the central identical points and without sharply

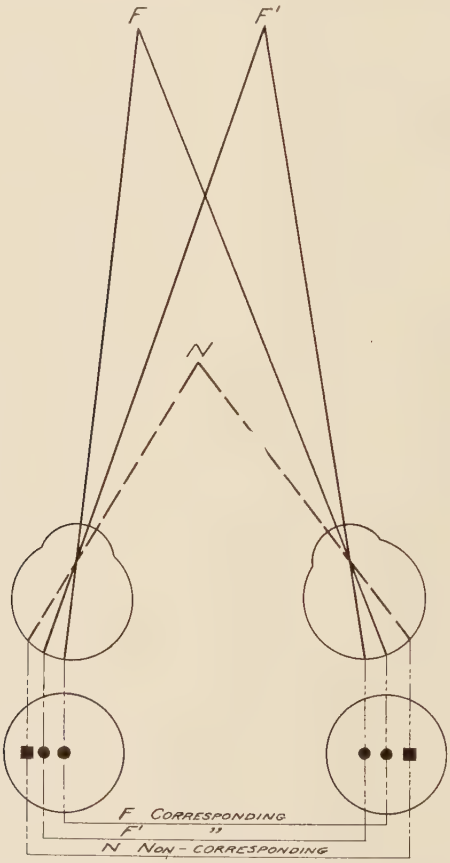

Fig. 116.—Physiological diplopia. F, the point fixed, with images in foveæ; F', a second distant point with images in corresponding points of two retinæ; N, near point with images (squares) on non-corresponding or disparate points.

defined boundaries. The probable actual sizes vary with the part of the retina; for central vision the corresponding area is perhaps 30 times the radius of the identical point which may as little as 3 μ or even 1 μ. Objects imaged on identical points are judged to be single and at the same distance as the point fixated, objects imaged on corresponding areas but not on identical points are judged single

and nearer if on the right side of the area of the right eye and the left side of the area of the left eye or farther if on the left side of the area of the right eye and the right side of the area of the left eye.

Diplopia is seldom noticed but the disparity of the images is interpreted as difference of position even when closer attention shows distinctly doubled images. What, then, might at first seem to be a defect in binocular vision, since similar images can only in special cases be presented to similar parts of the two retinæ, comes to be the source of our most delicate and rapid method of telling distance. Even disparations of less than 1 μ or about 5″ in the images cast on the more sensitive parts of the retina may cause the object to be judged nearer or farther than its fellows. Here again the fineness of perception appears to depend upon the mean of the response of a number of retinal elements, since a better judgment can be made of the position of a long thread than of a short one.

An interesting parallel to the conditions of binocular vision is furnished by the lips. If the edge of a card is pressed against the closed lips it is felt as single. If the lower lip is now drawn as far as possible to one side with the finger and the card again applied it is felt as double; as the lip is allowed to slip back toward a normal position the feeling of doubleness is finally lost but the single card is thought to be tilted and it is not felt to be upright until the normal relation between the lips is restored. Thus with lips there may be singleness combined with various degrees of tilting as with the eyes there may be single vision with varying degrees of distance.

The Stereoscope.—Since binocular disparity, or, as it is sometimes called, binocular parallax, appears as differences in the position of the parts of the two retinal images of external objects it is possible to duplicate these conditions by presenting different objects separately to the two eyes. An instrument for this purpose was first devised by Wheatstone and a later form by Brewster is familiar as the *stereoscope*. Since this instrument allows a clear analysis of binocular vision a brief account may be given. It is obvious that a pair of camera lenses separated by the ordinary interocular distance must give a pair of pictures differing exactly as do the retinal images. To present such a pair of pictures separately to the two eyes several conditions must be met. The photographs or diagrams actually used are somewhat more widely separated than the interocular distance; since in this way larger pictures are possible. To give the correct impression of size and extent a photograph should be viewed at a distance equal to the focal distance of the lens with which it was taken, but the eye cannot easily accommodate for so near an object. If the photographs are viewed through convex lenses they may be placed at the correct distance; by "decentering" these lenses a prismatic effect is introduced which allows the pictures to be more widely separated while the lines of fixation are

parallel or converged. Thus with the stereoscope the eyes may have normal conditions of accommodation and of convergence.

A pair of stereoscopic photographs differ so little that ordinary observation usually fails to show differences except in very near objects. The nature of these differences are clearest in a simple diagram. If a small pyramid is held before the eyes with the apex toward the observer, the right eye will see more of the right and the left eye more of the left side, giving two images represented at the top of Fig. 117. If these diagrams are placed in a stereoscope, the

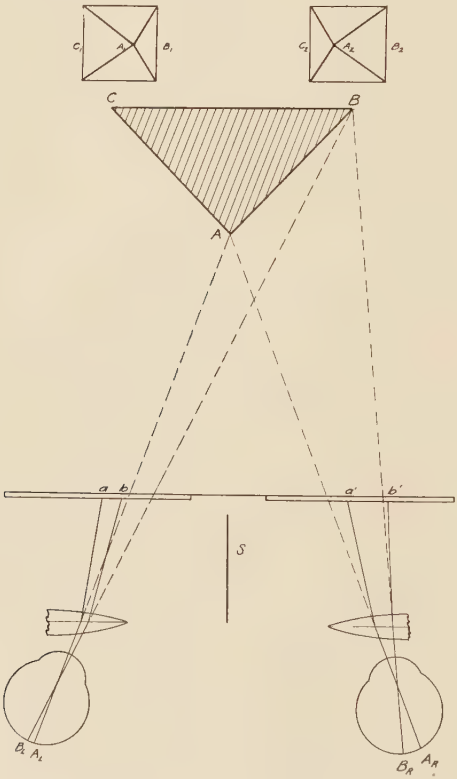

FIG. 117.—Diagram of Brewster's stereoscope. (See text.)

conditions are those represented in the remainder of the figure. At the bottom are horizontal sections of the right and left eyes as seen from above. Before the eyes are convex "half" lenses. S is a screen which prevents either eye from seeing the figure intended for the other. Axial rays from points b and b' of the diagrams entering the eyes and falling upon the right and left foveæ, B_R and B_L, appear to come from the point B on which the eyes are represented

as fixated. In the same way light from a and a' seems to come from A, and at $A\ B\ C$ there appears to be a pyramid.

Derangement of Binocular Movements.—As might be expected the delicate coördination of binocular movements is often impaired causing, if severe, obvious incoördinations of movement or, if less marked, latent tendencies to abnormal movements productive of much eye strain. It is beyond our scope to treat this complex phase of ophthalmology, yet so many of its features throw light both on binocular vision and on general questions of neuromuscular coördination that the main types of disturbance may be noted. Two types can be distinguished, *paralysis* and *squint* or *strabismus*, each with subdivisions.

Paralysis.—In paralysis there is a localized injury to the neuromuscular mechanism which prevents proper function. As a result binocular movements are carried out in part normally but are defective in some particular. Thus an injury to a single muscle or to its nerve as, for example, the lateral rectus or the sixth nerve will prevent or weaken the movements dependent on this muscle, the eye affected will be unable to turn laterally in a normal fashion but may keep pace with its fellow when turning nasally. The details may in each case be deduced from the action of the muscle or muscles concerned and present no features of special physiological interest.

Another form of paralysis results from injuries in the central nervous system, probably in the cortex. As previously stated a certain movement may become impossible, for example, the eyes cannot be turned to the left or converged while the muscles that might be suspected of incapacity function normally in other movements.

Squint.—In *squint*, the second and physiologically more interesting type of disturbance, the lines of fixation have an approximately constant although abnormal relation. With reference to fixation of a distant object Stevens introduced the following terms for the various relations.

Orthophoria, the normal parallel relation of the lines of fixation.

Heterotropia, a visible deviation from parallelism of the lines of fixation. Conjugate movements occur, both eyes moving to the right or to the left simultaneously but binocular fixation is not possible. Three forms are encountered:

(*a*) *Esotropia* or convergent squint (strabismus).

(*b*) *Exotropia* or divergent squint.

(*c*) *Hypertropia* in which the right or left line of fixation rises above its fellow.

Heterophoria, or latent squint, a tendency to non-parallelism of the lines of fixation, not visible because binocular fixation is habitually carried out when both retinæ are stimulated.

(*a*) *Esophoria*, a tendency to convergence of the lines of fixation.

(*b*) *Exophoria*, a tendency to divergence of the lines of fixation.

(*c*) *Hyperphoria*, a tendency of the right or the left line of fixation to rise above its fellow.

The heterotropias or manifest squints are readily seen, but the heterophorias are revealed only when the concealing fixation or fusion tendency is excluded. This is most readily done by fixating a distant object, such as a candle flame, and "covering" one eye with a card, that is, excluding the image from that eye and therefore the tendency to fixate. The covered eye will then take up a position dependent upon the joint influence of the centers governing conjugate movements and convergence. With orthophoria the line of fixation will be parallel to that of the fixating eye. With esophoria the eye will be seen to turn toward the nose when covered and to reassume parallelism when uncovered. At the instant of uncovering, the image will fall on the nasal side of the fovea and there will be a transient diplopia which vanishes with the movement of fixation.

Instead of excluding one image the two images may be made so dissimilar by distortion, as when a strong cylindrical lens or Maddox rod is placed before one eye, that they are treated as coming from two objects and not fused. Many instruments for eliminating binocular fixation and measuring the disparity of the images resulting from heterophoria have been devised; they are called *phorometers*. Although based on the above simple principle the details of operation may be complex.

The causes of actual or potential non-parallelism of the lines of fixation may be varied; it is not our purpose to treat them here. Obviously a congenitally small or weak muscle or assymmetrical orbits may give a physical basis. In a fairly common and physiologically very interesting type the squint results from the association between accommodation and convergence. As already stated accommodation and convergence normally occur in equal degree so that an object is seen clearly and single. If one eye is covered so as to exclude from it any stimulus to fixation or accommodation, it participates in convergence when the other eye is caused to accommodate as in trying to read fine print at a short distance. Under special conditions slight differences in the amount of accommodation and convergence may be forced at the expense of considerable effort. It therefore follows that the relation of the lines of fixation is linked with refractive defects. Thus, if a child with 4 D of hyperopia looks at a distant object he must accommodate 4 D to overcome his hyperopia and see clearly, yet at the same time he must not converge or he will see double. Such a degree of dissociation is usually not possible and the child is forced to see single but not clearly or double and clearly; the latter is often chosen, giving a marked squint. It is clear that a convex lens of 4 D correcting the refractive defect will restore the normal relation between accommodation and convergence and "cure" the squint.

If a serious incoördination of whatever cause is not corrected and results in visible squint, the confusion and discomfort of diplopia and the involved uncertainty of localization lead to vertigo, headaches and similar unpleasant consequences. Relief is found in ignoring the sensations from one retina and abolishing binocular vision, so that the person becomes physiologically one-eyed. For this reason squint of long standing cannot easily be cured; if the cause of the heterotropia is removed the coördinations of binocular vision must be patiently relearned.

Features of Binocular Vision Other than the Perception of Distance.—Although the chief contribution of binocular vision is to the perception of distance, there are other respects in which vision with two eyes is superior to that with one. If, as in the normal use of the eyes, similar images are presented to corresponding points of the two retinæ, the binocular threshold for light is usually less than for either eye alone. This is particularly true in partial or complete dark adaptation in which it may actually be possible for the two eyes to see a light of only half the intensity that can be seen with either eye separately. This effect is called *binocular summation*. With good light adaptation this appears to be absent.

That some superiority of binocular vision still exists in light adaptation is indicated, however, by the common experience that the use of both eyes always increases the visual acuity over that possible for either. With moderate indoor illumination this might result from the greater brilliance due to binocular summation, but it seems to occur even with complete light adaptation.

If, on the other hand, dissimilar images are presented to correponding points of the two retinæ the results are different. Usually the two forms or hues are perceived alternately or prevail locally in certain parts giving a patchy and fluctuating visual field, an effect known as *retinal rivalry*. It is probably due to cortical activity and is associated with shifts of attention. Certain persons under special conditions obtain binocular mixtures of hues separately presented to the two eyes. Vision in general is distinctly impaired by dissimilar images on the two retinæ.

Summary.

Differences in the structure of certain regions of the retina are significant in considering their functions; the most important of these regions are the *papilla* of the optic nerve, the *macula lutea*, the *rod-free area* and the *fovea centralis*. The rods and cones of the neuroepithelium exceed in number the fibers of the optic nerve by 100 or 200 to 1, the actual relation differs in different parts of the retina, being approximately 1 to 1 in the fovea and becoming more multiple toward the periphery. The rods and cones are the essential receptors.

When visible radiations of proper intensity fall on the retina they cause photochemical changes which modify the functional metabolism and give rise to reflexes and sensations. Only a few objective changes can be demonstrated in the retina. These include the movement of pigment (questionable in mammals), bleaching of the visual purple in the light, and changes of electrical potential.

The *visual sensations* are more numerous and varied than those of any other receptor. The attributes peculiar to visual sensations are *brilliance, hue* and *saturation;* in common with other sensations they may have *extensity, duration* and show *temporal* and important *spatial relations.*

Brilliance (the intensity attribute) depends on (*a*) the physical brightness and wave length of the light and (*b*) the part of the retina stimulated, the previous stimulation of this part and the simultaneous stimulation of other parts. The extraordinary power of *adaptation,* determined by previous stimulation, enables the eye to function satisfactorily for light intensities varying through the enormous range of two or three million fold. This capacity for changing the sensitivity is most satisfactorily explained by the "duplicity" theory which assigns to the cones perception of brilliance and chromaticity in bright lights and to the rods the perception of brilliance over a wide range of dim lights through the action of visual purple.

Local adaptation causes changes of sensitivity in those parts stimulated by different intensities of the image, so that the retinal response is not uniform to subsequent uniform stimulation giving rise to transient *"after-images."*

The retina has less inertia than most receptors, yet neither the beginning nor the end of the sensation are synchronous with the beginning or the end of the stimulus. Because of this, rapidly repeated stimuli *fuse* to a continuous sensation with a brilliance which is the average of the brilliance produced separately by the component stimuli.

The brilliance of a sensation is influenced by the simultaneous stimulation of adjacent parts of the retina; this effect is known as *contrast.* A stimulus flanked by a less intense stimulus gives a more brilliant sensation than when flanked by more intense stimuli.

A change of about 2 per cent in the intensity causes a perceptible change of brilliance over a wide range of intensity, a striking example of Weber's law.

The chromaticity of the sensation (hue and saturation) is dependent upon (*a*) the nature of the stimulus and (*b*) the state of the retina.

Radiation containing all the frequencies in the proportion found in sunlight give sensations devoid of chromaticity (white or gray); single frequencies as in the spectrum give *hued sensations* of which

about 130 can be distinguished. The simultaneous or rapidly alternating stimulation of a part of the retina with 2 or more frequencies is called *color mixing;* the hue perceived may be (*a*) the purples, not in the spectrum, (*b*) spectral hues (as red and yellow give orange), or (*c*) white or gray. Pairs of frequencies giving white are said to be complementary colors. Radiations of a single frequency give a *saturated* sensation, admixture of white light makes the sensation less saturated until at last it cannot be distinguished from gray, when it is said to have zero saturation and no hue.

The chromaticity of the sensation from any stimulus is affected as is brilliance by the part of the retina stimulated, the previous stimulation of that part or the simultaneous stimulation of adjacent parts. The fovea is most sensitive to chromaticity, the periphery distinguishes hues only with difficulty. The after-image of objects giving hued sensations may be the hue of the original sensation (*positive*) or the hue complementary to the original sensation (negative). *Contrast* tends to give a complementary hue. The chromaticity of the sensation of certain people differs markedly from the normal; such persons are called *color blind.* The totally color blind perceive brilliance but no chromaticity. Other persons perceive hue but differ from the normal in that all the perceivable hues can be matched in color mixing by two frequencies, whereas the normal requires three. They are therefore said to have *dichromatic* in contrast to the normal *trichromatic* vision. In a common form which is congenital and inherited as a sex-linked character appearing in 2 to 4 per cent of males but less than 1 per cent of females, reds and greens are readily confused. Since these hues are used as signals on railways and boats, examination of prospective operators is regularly carried out on thousands of men.

Various hypotheses have been proposed to explain the perception of chromaticity. Of these the Young-Helmholtz, Hering and Ladd-Franklin hypotheses are most prominent, but neither can be considered as final.

Sensations of whatever brilliance, hue or saturation show important spatial relations which are considered under the heads of *extensity, direction, form, motion* and *distance.*

Direction, the primary form of perceived spatial relationship depends on the local sign of the retina and the sensation from the motorceptors of the eye muscles. The fineness of local sign or "resolving power" of the retina varies widely, being highest in the fovea and falling off rapidly in all directions toward the periphery. In the fovea the separation of parallel lines that can just be perceived corresponds closely with the histological data on the cones, a space of 3.3 μ serving to distinguish lines.

Eye movements are accomplished by the six muscles which turn the eye in the pad of orbital fat very much as the head of a bone in a

ball-and-socket joint. Physically movements of some extent are possible about any axis, physiologically they are greatly limited in accordance with certain features of the use of the eyes. Monocular movements serve to *fixate* an object, that is, so to turn the eye that the image falls in the center of the fovea. The *field of fixation* or totality of points that may be so fixated without moving the head is about 100° in vertical or horizontal extent. Rotation about the *line of fixation* passing from the object fixated through the center of rotation to the fovea does not occur except to a slight extent reflexly, when the head is tipped down on the shoulder. The action of the individual muscles is known but is complex and differs for each position of the eye. Probably all the muscles participate in each movement of the eye in one of the following capacities (*a*) (*a*) *prime movers*, (*b*) *synergists*, (*c*) *fixation muscles* and (*d*) *antagonists*. This organization into a muscle pattern occurs apparently at cortical levels. Several types of eye movements may be distinguished, of which the *pursuit* and *saccadic* movements are the most important. The former maintains fixation on a slowly moving object, the latter serves to fixate an object seen indirectly. The movements present a mixture of voluntary and reflex characteristics; they may be executed on command and have the time of voluntary movements but are often unconscious and in the saccadic type have a rate that cannot be altered voluntarily.

All movements subserve fixation and seem related to the sensory gradient presented in a high degree by the retina. This gradient of which the fovea is the morphological culmination is fundamental for the perception of direction and for binocular vision.

On the two-fold basis of retinal local sign and motor sensation all objects are localized in terms of direction; that is, the direction in which the hand must be moved to touch an object is correctly perceived when the object is seen. This is independent of the position of the retinal image and would have developed had the position been other than it is.

The perception of *form* depends on the perception of direction and is limited by the same factors.

Motion may be perceived as successive positions but also apparently directly. Like visual acuity it declines in peripheral vision, although not so rapidly.

Distance is perceived in part from monocular clues but most directly and accurately from binocular parallax. The important monocular clues are apparent size, aerial perspective, shadows and interventions, accommodation and monocular parallax.

Binocular vision involves binocular movements giving simultaneous fixation with both eyes. Most movements are *conjugate*, the two lines of fixation remaining parallel; this type has a deep-seated nervous basis, occurring soon after birth and persisting in

complete blindness of one eye. Of the *disjunctive* type in which the axes are not parallel, *convergence* is the only one normally carried out.

Ordinarily objects although giving two images, one on either retina, are seen as *single*, although *double vision* or *diplopia* may also occur. The retinal relations involved in single or double vision are as follows: Corresponding points are pairs of points, one in each retina, the simultaneous similar stimulation of which give rise to single perceptions. *Non-corresponding* or *disparate* points are similarly those which give rise to double perception or diplopia.

The general relation is that corresponding points would agree in position if the retinæ were superposed with coincident lines of fixation and without rotation about these lines.

Similar images on corresponding points are referred to the same direction and thus to the same object. This is preëminently true of the foveæ.

From geometrical necessity objects at different distances will not fall on geometrically superposable points but with moderate disparity they are not perceived as double but as nearer or farther. We must therefore consider corresponding points as small areas, and that if the right side of the corresponding area of the right and of the left side of the area of the left eye are stimulated the object is judged nearer or, if the reverse condition occurs, farther.

The *stereoscope* is an instrument to give binocular perception of distance by presenting separately to each eye pictures differing in the same way as the two retinal images normally differ.

Derangements of binocular movements often occur. *Paralyses* result from injuries to individual muscles or to centers giving one type of movement. *Squint* in which the lines of fixation are not or tend not to be parallel may result from various conditions of which the most interesting physiologically is that dependent upon the association between accommodation and convergence. This may lead a hyperope to converge excessively as he attempts to overcome his hyperopia by accommodation.

The binocular threshold for light, particularly in the dark-adapted eye, is less than for either eye alone.

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CHAPTER XXXVII.

NEUROMUSCULAR FUNCTIONING: POSTURE.

Animal Behavior—the Sum Total of Bodily Reactions.—In the last few chapters the operation of the various receptors has been considered in detail. They have been shown to vary greatly in specific manner of functioning, yet all to serve one definite purpose, viz: to translate environmental influences of one sort or another into streams of afferent impulses. These afferent streams are translated, in turn, into efferent streams whose effect is to evoke bodily reactions (page 127); the latter, in sum total, constituting the *behavior* of the organism.

The conversion of afferent impulses into efferent is the function of the central nervous system. In very large part, as already pointed out, the conversion is automatic, forming the basis of reflex action (page 120). When the behavior of one of the higher animals is studied, however, much of it is found not to accord with the description of reflex action, as given in Chapter VIII. Evidently additional factors enter to determine the reactions of the higher organisms to the situations in which they find themselves.

The reactions of a higher organism are accomplished through activity of effectors, working in nicely coördinated and frequently very complex "muscle patterns." Underlying the reactions, and in fact making many of them possible, are certain neuromuscular relationships which must be stated before the reactions themselves are studied further.

Nicety of Response Related to Delicacy of Innervation.—The effectors are either skeletal muscles, smooth muscles, the cardiac muscle of the heart, or glands; our bodies contain no other tissues which can function actively in response to influences from outside themselves and in so doing contribute to adjustment. In an earlier chapter (page 129) attention was directed to an important difference between skeletal muscles and all other sorts of effectors in respect to the definiteness and exactness of the adjustments that can be made. Skeletal muscle, as was there pointed out, operates on the basis of small units, and hence is capable of very sharply localized and exactly graded activity. Smooth and cardiac muscle and gland tissue, on the other hand, operate more in mass. These differences are due in part to the inherent characteristics of the tissues, but in equally large part to the way in which they are innervated; it is with this latter point that we are now to be concerned.

DISTRIBUTION OF MOTOR NEURONS.

Every fiber of skeletal muscle in the body is connected with a motor neuron (page 140). These neurons arise from cell bodies in the ventral horns of gray matter of the cord, or from corresponding regions of the brain. They pass in spinal nerves, by way of the ventral roots, out to the peripheral nerve trunks, by which they are distributed to their destinations. (In the head by equivalent cranial nerve trunks.) Upon reaching the skeletal muscle mass every axon subdivides into a number of branches, each of which connects with a single muscle fiber. The number of branches probably varies in different muscles in accordance with the fineness of gradation of effort of which they are capable; the eye muscles and the muscles of the vocal apparatus, for example, would be likely to show a smaller ratio of muscle fibers to axons than would the trunk or limb muscles. In the few counts which have actually been made fifteen to twenty muscle fibers have been found for each nerve fiber.

MYONEURAL JUNCTIONS AND THE EFFECT OF CURARE.

The visible connection of motor nerve branches with skeletal muscle fibers is by means of structures called end-plates. These are thought to be in reality part of the nerve terminals, since they degenerate along with the axon whenever the latter is cut across. The true myoneural junction, corresponding in function to the synapse, is between the end-plate and the contractile substance of the muscle fiber. Various views as to the nature of the myoneural junction have been held. It seems to function, very much as does the synapse, as a region of difficult and delayed conduction (page 112). It shows, also, certain special properties that synapses do not share. For example, the drug curare in moderate doses does not impair either nervous or muscular functioning, but does prevent disturbances from passing across the junctions between motor nerve and skeletal muscle fibers. The effect upon an animal is, of course, complete paralysis of the skeletal musculature. Certain South American Indian tribes have used crude curare as a poison for arrows and spears for an unknown, probably very long, time. This property of curare was employed early in physiology to demonstrate the "independent irritability" of muscle, that is, the ability of muscle to respond to stimulation received directly and not through the nervous system.

Selective Innervation of Muscle Fibers.—The significance of myoneural junctions in neuromuscular functioning arises from the fact that they may operate like synapses, to determine which of a number of possible paths propagated disturbances may follow. If

we take the number of branches of a single motor axon to be twenty there are twenty junctions potentially traversable by the impulses arriving over the axon. The junctions may all offer resistance to the passage of impulses, and if the degree of resistance varies it is possible that some junctions may be crossed and others not. In other words, there is a possibility that not all the muscle fibers innervated by a single motor axon are actually excited to contraction every time impulses pass along the latter. Whether this possibility is ever realized depends on whether differences in resistance really do occur. There is definite evidence that fatigue increases the resistance of myoneural as well as of synaptic junctions. Muscular fatigue, as we have already seen (page 90), probably results from accumulation of metabolic products within the fibers, which accumulation, in turn, is due to the failure of the oxidation processes and of waste product removal to keep pace with the antecedent stages in metabolism. If the blood supply to all the fibers were exactly uniform we might expect them all to become fatigued at the same rate, but, as has already been pointed out (page 341) it is now known that the blood flow through the capillaries is exceedingly variable. It may happen that fibers whose myoneural junctions are in a state of such fatigue that impulses cannot pass them receive an access of blood, through the opening of capillaries previously closed; this enables them to recover rapidly, so that they become once more open to stimulation. At the same time the junctions leading to functioning fibers are becoming fatigued, and presently will no longer pass impulses. The result is a shift of performance from one set of fibers to another. It is believed that this goes on regularly in muscles that are being kept in action more than momentarily. It is an automatic arrangement for distributing the burden, and so preventing undue fatigue of individual fibers.

SKELETAL MUSCLE TONUS.

The fact has long been known that the resting skeletal muscles in the intact body are normally in a state of continuous slight contraction superficially similar to the tonus of smooth and cardiac muscle (page 93) and designated *skeletal muscle tonus*. This type of tonus is immediately dependent on the nervous system, disappearing promptly from any muscle whose nervous connection with the cord is cut. It is evoked reflexly, the afferent part of the reflex being predominantly of proprioceptive origin (page 498).

Sherrington and co-workers have demonstrated the existence of a definite highly localized tonus inciting reflex, which they designate the *myotatic* reflex. The adequate stimulus is simple stretching of the muscle, a stimulus which excites proprioceptors. The reflex is very exactly graded, both as to *locus* and *intensity*. If only part

of a muscle is stretched only that part develops reflex tonus; if the stretching is slight the tonus is correspondingly feeble; as the stretch is increased, the tonus increases to correspond. None of these responses occur in a muscle deprived either of the afferent nerves from the receptors imbedded in it or of the efferent nerves by which it is stimulated, thus proving the action to be reflex and to be mediated by the muscle's own proprioceptors.

Theories of Tonus.—The precise nature of skeletal muscle tonus is uncertain. The known facts about the structure and mode of action of skeletal muscle fibers (page 79) appear not to admit of partial contractions similar to those conceived to form the basis of smooth muscle tonus. Two alternatives accordingly suggest themselves: (1) That special *tonus* fibers are interspersed among the true contractile fibers; (2) that tonus of the entire muscle is maintained by *ordinary tetanic contractions* of a small fraction of the fibers, fatigue being prevented by a shift of activity from one set of fibers to another in rotation (A. Forbes).

The conception of special tonus fibers receives some support from the histological demonstration in lower vertebrates of small reddish striated fibers among the larger and paler, definitely contractile fibers, the former making contact with autonomic (non-myelinated) axons, the latter, in typical fashion, with somatic axons through motor end-plates. Although birds and mammals have two kinds of muscle fibers, one pigmented (the *red* fibers) and the other non-pigmented (the *pale* fibers), it is fairly clear that both are actively contractile. Furthermore both types are frequently, if not invariably, in contact with terminals of autonomic nerves, in addition to their somatic innervation (Tschiriew and others).

Some investigators have reported observing a loss of tone in muscles after severing the *autonomic* nerve supply to them, leaving the somatic supply intact; but in every case the tonus has disappeared only after several days, an observation strikingly different from the prompt disappearance of tone, when the entire efferent connection, both somatic and autonomic is severed. The indication is that the autonomic supply to a muscle is concerned with its nutrition rather than with the direct maintenance of reflex tonus. This conception is strengthened by the observation of Orbeli that muscles contract more forcibly when the autonomic nerves supplying them are stimulated while they are being excited through their motor nerves than when autonomic stimulation is omitted. This is true to some extent of muscles deprived of their blood supply. Consequently the action is in part exerted directly on the muscle fibers and cannot be due entirely to improvement in the circulation.

The alternative conception, that tonus is due to tetanus of a fraction of the fibers, is in full harmony with the all-or-nothing

principle of muscular action (page 85). It can be accounted for in accordance with known facts of synaptic fatigue (page 114) and myoneural junction fatigue (page 691). Thus whenever the reflex is established the group of muscle fibers reached by the least fatigued pathway is necessarily the one first excited. Fatigue of synapses or myoneural junctions or both quickly raises the resistance of this path, but meanwhile other paths are recovering from former fatigue, and so become passable, to be utilized for a brief period and then closed in their turn by fatigue, to be succeeded by still others. In the present state of our knowledge this second conception must be preferred to the first.

Relation of Tonus to Posture.—The great significance of skeletal muscle tonus as a factor in bodily functioning is in its bearing on the maintenance of *posture*, in other words, on the mechanism by which the body or any part of it is held in any position other than that of complete relaxation. The point has already been stressed that the holding of a definite posture implies (in a land animal) resistance to the tendency of joints to bend or parts of the body to sag. Either of these tendencies necessarily puts muscles on the stretch. If the stretching fails to be counteracted the posture is lost. Consequently we see in the myotatic reflex a remarkable automatic mechanism for causing posture to be maintained.

An analysis of posture shows it to be predominantly a function of *extensor* muscles, shared to a considerable extent by adductors and abductors; muscles of these classes are normally in decided tonus. Flexors show much less, the main examples of flexor tonus in man being seen in the flexors of the fingers when the hand is at rest. All the eye muscles are in tonus during waking, as are also the muscles that close the jaw. Tonus is more or less in abeyance during normal sleep—a factor of undoubted importance in making sleep a valuable restorative.

Tonus the Background of Muscular Activity.—To appreciate the great significance of postural tonus one must realize that it forms the background against which every motion of skeletal muscles is made. The remarkable deftness with which most movements are performed depends on accurate tonus adjustments of muscles not primarily concerned in making the movements, but associated with those that are. For example, flexion of the fingers without accompanying wrist flexion is achieved by a simultaneous heightening of the tonus of the wrist extensors (the *fixation* action of opposing muscles, page 669).

Reciprocal Innervation.—An interesting case of an adjustment that facilitates muscular action is the *decline or disappearance of tonus* from a muscle when its opponent is reflexly excited to contract. This phenomenon, studied extensively by Sherrington, is particularly

easy to demonstrate experimentally in the extensors, by initiating flexor reflexes. It is explained as due to so-called *reciprocal innervation of antagonistic muscles.* The phenomenon implies that the reflex path over which any skeletal muscle may be excited includes two parts: One, the excitatory path proper, which is thought to be organized according to the general plan already described (page 120); the other, a collateral path, by which the prevailing tonus in the opponent may be lessened or even abolished. The latter path is conceived to be so organized that impulses excitatory to the primary muscle also impinge, through collaterals, on synapses in the efferent path to the opponent. This path is traversed normally by the steady stream of efferent impulses by which tonus is maintained (page 691). The impingement of a second stream, under the circumstances just described, necessarily increases the frequency with which impulses bombard the particular neurons with which the collaterals make contact. This can easily be conceived to have the effect of reducing the size of individual impulses in these neurons, in extreme cases, so materially as to prevent any at all from passing on to the next neurons in the sequence (page 125).

Although described as a feature of reflex action, reciprocal innervation has been found to accompany most volitional movements as well. It is important to note that the feature of *serviceability* is retained in this as in other bodily adjustments. Thus, nearly all *delicate* movements depend for their successful accomplishment on the persistence of a definite degree of tonus in the opposing muscles, to prevent the primary muscles from "overshooting." Corresponding with this necessity we note that reciprocal innervation does not imply a complete disappearance of tonus in movements of this type. Its value is clear, in that it obviates the necessity that contracting muscles overcome unnecessary drag of their opponents in addition to performing the primary tasks for which their contractions are evoked.

Widespread Influence of Certain Proprioceptors.—While the myotatic reflex is an important factor in tonus (page 691), its action is purely local, not extending beyond the muscle or portion of a muscle within which lie the proprioceptors by which it is evoked. The non-acoustic labyrinth (page 504), on the other hand, is an important proprioceptor from which impulses arise by which the tonus of the entire musculature may be affected. The proprioceptors of the neck muscles have a similarly widespread influence. The existence of effects from these proprioceptors, extending to all parts of the body, implies an organization in the central nervous system by which they are mediated. In gross, this organization is conceived to consist of "tonus centers" located in the brain stem and anterior portion of the spinal cord (Magnus).

DECEREBRATE RIGIDITY.

In many species of animals, notably cats, cutting across the brain stem at the level of the superior colliculi (the operation of *decerebration*) results in a marked accentuation of postural tonus, with the result that the limbs become unexpectedly rigid. Thus, the limb tonus of a decerebrate cat lying on its back, or suspended in a sling so that its feet clear the floor, may be as decided as of a normal cat supporting its weight in the standing posture, although in the decerebrate animal on its back or in a sling no particular stretch is put on the muscles, consequently the myotatic reflexes are less strongly aroused, and an important source of afferent impulses for maintaining tonus reflexes is missing.

The phenomenon is interpreted as proving two important facts about the tonus mechanism, additional to those previously described: (1) That the volume of afferent impulses of general proprioceptive origin (perhaps reinforced by asymmetric skin stimulation, page 509) is potentially adequate to maintain marked tonus, particularly of the postural muscles, without extensive coöperation from myotatic reflexes (these cannot be dispensed with altogether, as shown by the fact that cutting the afferent connections between any muscle and the central nervous system results in prompt and irrecoverable loss of tone within it); (2) that a stream of impulses normally descends continuously from the cerebrum, *depressant* to the tonus mechanism as a whole. Thus, as long as the cerebrum is intact *general tonus* is so materially depressed that it does not maintain posture effectively unless reinforced by active myotatic reflexes. When, however, impulses from the cerebrum are prevented from exerting their influence the general tonus rises to an effective level, the extensor rigidity characteristic of the standing posture being then present in the limbs of non-standing animals. Transecting the brain stem at the level of the lower half of the bulb abolishes rigidity at once, due to cutting the connection between the brain stem centers mentioned above and the musculature.

CEREBELLAR FUNCTION.

Nothing reveals more clearly the fundamental importance of delicately coördinated muscular activity as a feature of animal behavior than the existence in all vertebrates of a special subdivision of the brain, the *cerebellum*, functioning as a regulatory center for the entire neuromuscular mechanism. The organ appears to be in reality a *group of centers*. It receives afferent impulses from all proprioceptors of the body; from those of muscles, joints and tendons, by way of the dorsal and ventral spino-cerebellar tracts; from the labyrinths, by way of the vestibular nerves. These afferent

paths terminate in the *cortex* of the cerebellum, by establishing synaptic connection either with the Purkinje cells (through "climbing" fibers) or with the granule cells (through "mossy" fibers).

Evidence indicates that axons of the vestibulo-cerebellar tracts connect with cells of one type and axons of the spino-cerebellar tracts with cells of the other, although the significance of this difference is not yet known (Fig. 118). Paths from the cortex of the cerebrum (page 700) to the cerebellum also exist (the cortico-pontine tracts).

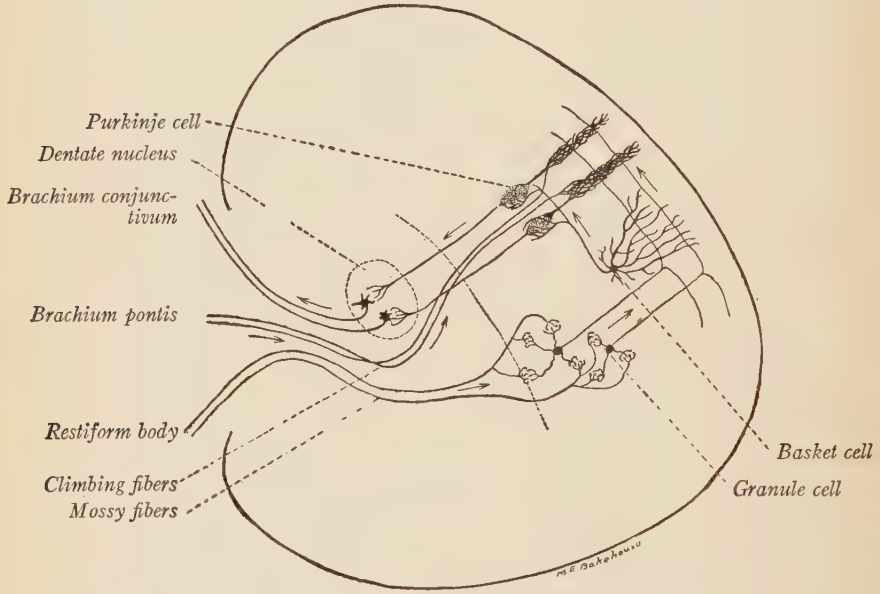

FIG. 118.—Diagram to indicate the probable paths of conduction through the cerebellum. (From Ranson's Anatomy of the Nervous System, W. B. Saunders Company, Publishers).

From the cortex of the cerebellum efferent paths lead (mainly by way of the dentate nucleus and brachium conjunctivum) to the mid-brain (red nucleus mainly) and cord and thence to ultimate termination in synaptic connection with the cell bodies of presumably all the somatic motor neurons of the body. The connections are *homolateral;* that is to say, paths from the left cerebellar cortex communicate with motor neurons in the left side of the brain stem or cord and *vice versa.*

The effect of the efferent discharges from the cerebellum is conceived to be, as indicated above, to modify reflexes and direct volitional discharges in such a manner as to ensure that the various

muscle groups involved shall function in accurate coördination. This conception implies that the cerebellum may, on occasion, function to *depress* the tonus set up by direct proprioceptive reflexes. This depressant function has been demonstrated experimentally (F. R. Miller). It is manifested, following certain types of cerebellar injury, by a period of heightened tonus in some muscles (Luciani), in consequence of the destruction of the paths over which the depressant influences normally pass. The most important effect of cerebellar injury is imperfect control of the muscles (astasia). A state of chronically reduced tonus (hypotonia) is commonly seen, but this now appears to be due to injury to delicate structures underlying the cerebellum; hence does not imply, as formerly thought, that the organ has a tonus-maintaining function. There is also marked weakness (asthenia), the reason for which is not clear.

Summary.

The *behavior* of one of the higher organisms is made up of reactions to environmental situations, some of which are typically reflex in character, while others involve additional factors, not present in automatic reflex actions.

Animal reactions consist of highly coördinated muscular acts, whose effective performance depends on the existence of certain definite neuromuscular relationships summarized below.

Every skeletal muscle fiber is innervated through a *terminal branch* of a motor neuron. Such counts as have been made show 15 to 20 individual muscle fibers on the average for each motor neuron.

Myoneural junctions appear to resemble synapses in offering resistance to the passage of disturbances across them. They differ in being specifically susceptible to curare, a drug which in moderate doses blocks myoneural junctions without injuring other structures significantly.

Myoneural junction fatigue may block the passage of impulses from nerve fibers to muscle fibers. Inequalities in the blood supply to individual fibers may result in unequal degrees of fatigue, hence impulses over a given axon may excite part of the muscle fibers with which it connects and fail to excite the remainder.

Skeletal muscle tonus is a continuous slight contraction of skeletal muscles, maintained reflexly, the afferent stimuli being mainly proprioceptive.

Simple stretching of muscles evokes highly localized and exactly graded tonus reflexes within the stretched muscles, designated as *myotatic reflexes*.

The weight of evidence indicates skeletal muscle tonus to consist of *ordinary tetanic contractions* of a small fraction of the fibers, acting in rotation. An alternative theory postulates special tonus fibers interspersed among the contractile; the tonus fibers innervated through the autonomic system. A more likely view is that the

autonomic innervation is concerned with the metabolism of the muscle fibers rather than with the maintenance of tonus in them.

Skeletal muscle tonus is significant as the basis of *posture*. It is most marked in the extensor muscles; clearly shown in adductors and abductors; least manifest in flexors. It forms the essential background to all muscular activity.

A feature of many reactions is decline in or disappearance of tonus from the opponents of the muscles that perform the actions. The phenomenon implies the existence of *reciprocal innervation to antagonistic muscles*. A suggested explanation postulates collaterals from neurons in the excitatory path, impinging through synapses upon neurons in the tonus-maintaining path to the opponent. The increase in frequency of the impulses thus introduced into the latter path is assumed to be so marked as to reduce individual impulses below the level of effectiveness.

The non-acoustic labyrinth and the muscles of the neck contain proprioceptors which influence the tonus of the entire musculature. The effects are mediated through *tonus centers* in brain stem and anterior cord.

The operation of *decerebration* (transecting the brain stem at the level of the superior colliculi) results in a heightening of postural tonus, designated *decerebrate rigidity*. The phenomenon is interpreted as proving: (*a*) That the *general tonus* reflexes, mediated through brain stem centers, are potentially adequate to maintain posture with only moderate reinforcement from myotatic reflexes; (*b*) that a stream of depressant impulses normally descends continuously from the cerebrum, preventing the general tonus reflexes from developing to their full extent.

The *cerebellum* receives afferent impulses from all the proprioceptors of the body and discharges efferent impulses homolaterally to (presumably) all somatic motor neurons.

Efferent impulses of cerebellar origin may depress the tonus level set by the direct proprioceptive reflexes. The main action of the cerebellum is conceived to be to cause the various muscle groups concerned in complex reflex or volitional activity to function in accurate coördination. Muscular weakness (*asthenia*) and imperfect control of the muscles (*astasia*) are after effects of cerebellar injury. The *hypotonia* also commonly seen is now thought to be due to injury to non-cerebellar structures.

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CHAPTER XXXVIII.

THE CEREBRUM: GENERAL FUNCTIONS AND CONNECTIONS.

DELAYED RESPONSE A FACTOR IN BEHAVIOR.

When attention is directed to the *sensory basis of behavior,* in other words, to the way in which the receptors play their part in determining what activities animals shall show from moment to moment, the subdivision of the exteroceptors into contact receptors and distance receptors (page 480) takes on particular significance. Receptors of the first group are specialized to respond to stimuli that arise from sources directly at the surface of the body. Thus, touch, pain, taste, the temperature senses and some others are excited only by agencies directly upon or within the body; response to stimulation of receptors of this group must generally be prompt to be serviceable. In the case of the distance receptors, smell, hearing and sight, on the contrary, the actual features of the environment from which stimulation is derived may be quite far removed from the body; when this is true some delay in responding will not necessarily imperil the success of the reaction. We recognize, then, one class of receptors which calls for prompt responses and another class which may permit of some delay. The importance of this factor of possible delay is that it introduces an additional factor, that of *selective reactivity* or *choice*, which is bound to be of great benefit to the organism, provided advantage can be taken of it.

It is clear that responses that must be prompt must also be quite automatic ordinarily if they are to be serviceable. Only if no harm is likely to result from delay will an animal be better off for being able to select between several possible responses. On the other hand, granting that delay is safe, there is clearly great advantage in the possession of a mechanism for making selection from among several serviceable reactions. The type of nervous action which we call *volitional* has its foundation in a mechanism of this sort.

DISTANCE RECEPTORS AND THE BRAIN.

Features of the distance receptors that are much stressed in connection with attempts to picture the mechanism of selective reactivity are: (1) Their complexity, all of them consisting of many receptor units, each of which has its own receptive neuron

connection with the central nervous system; (2) their common location at or near the front end of the body. It is clear that the part of the body that comes first into a new environment as the animal moves about is the most advantageous location for distance receptors. One effect of the grouping of these complex sense organs into a single region is that the underlying ganglia of the central nervous system, into which all the receptive neurons from them must lead, will necessarily be disproportionately large, and likewise disproportionately rich in synaptic junctions, in comparison with other parts of the central nervous system. Thus, hand in hand with the special features of the distance receptors goes a specialization of the associated part of the central nervous system into a *brain*.

Synapses Particularly Numerous in the Cerebral Cortex.—The brain is noteworthy for the exceptional richness of its synaptic connections. This richness is in part due, as just pointed out, to the disproportionately large ingress of receptive neurons to the region, but much more to the presence in portions of the organ, notably the *cortex* of the cerebrum, of enormous numbers of internuncial neurons whose branchings are very numerous. So far as we can judge from the evidence thus far obtained, the machinery for exercising choice resides chiefly if not exclusively within the cerebral cortex, a region of abundant and richly interconnected internuncial neurons. The first steps in analyzing the function of the cerebral cortex are obviously to determine its relationships with other portions of the central nervous system, and, so far as possible, to group the neurons of which it is composed in accordance with their functions.

THE CEREBRAL CORTEX.

The cerebrum, by far the most massive subdivision of the nervous system in all higher organisms, weighs about 1200 to 1500 gm. in man, as compared with 25 to 35 gm. for the spinal cord and 160 to 170 gm. for the cerebellum. It is interesting to note, by way of contrast, that in the frog the brain and cord are about equal in weight. The human cerebrum presents a total surface estimated at about 2000 sq. cm. (H. Wagner), of which fully two-thirds is to be accounted for by the convolutions. The *cortex* is a layer of gray matter (cell bodies and synapses) about 2 mm. thick, covering the entire surface, including the mesial aspect of each hemisphere, and the islands of Reil, concealed from external view within the Sylvian fissures. The total number of cell bodies in the cortex is inconceivably enormous, to be reckoned undoubtedly in billions. A fact of significance is that the cell bodies are on the average further apart in man than in any other form. In other words, the human cortex has the least number of cells per unit volume of any organism. This means that synaptic connections are more numerous and richer in man than in other species; for the

room in the cortex not taken up by cell bodies is occupied by dendrites and terminal arborizations of axons. This exceptional wealth of intercommunication among neurons is looked upon as

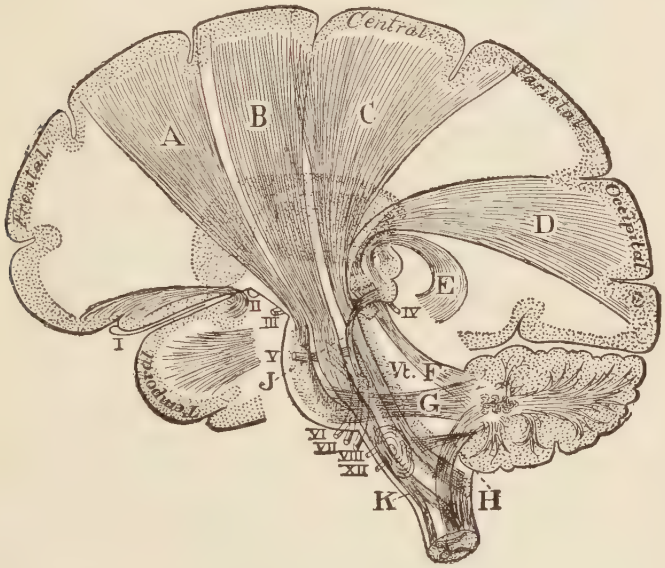

FIG. 119.—Diagram showing projection fibers of cerebrum. (From Starr.) (Martin's Human Body, Henry Holt & Co., Publishers.)

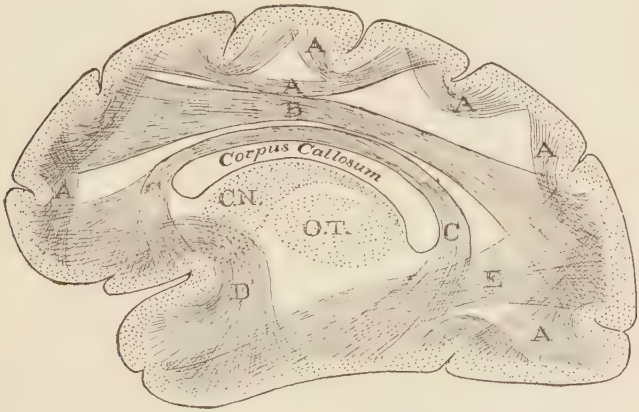

FIG. 120.—Diagram of association fibers of cerebrum. (From Starr.) (Howell's Physiology, W B. Saunders Company, Publishers.)

in all probability an important factor in the intellectual superiority of man over the lower animals, the inference being that the more connections each neuron can make the more elaborate are the mental processes of which the organism is capable.

The Cerebral White Matter.—Underlying the cortex is the white matter of the cerebrum. This consists of myelinated axons. Three distinct groups of the latter are recognized: (*a*) *Projection fibers* (Fig. 119), including all axons by which connections are made between the cells of the cortex and other parts of the nervous system; (*b*) *association fibers*, including all axons by which connections are made among cortical cells themselves *within the confines of a single hemisphere* (Fig. 120); (*c*) *commissural fibers*, including all axons by which cortical cells in one hemisphere make connection with cortical cells in the other.

Afferent and Efferent Projection Fibers.—The projection system as a whole includes all the pathways of the cerebral white matter by which nerve impulses may impinge upon the cortex from any source outside itself and also all by which impulses may pass from the cortex to impinge on non-cortical structures. The first group, made up of *afferent* projection fibers, constitutes the final rank of a sequence of afferent neurons by which the various receptors come into communication with the cortex. The second group, composed of *efferent* projection fibers, is similarly the initial rank of a sequence of efferent neurons by which the cortex is able to exert influence on the effectors.

CLASSIFICATION OF AFFERENT PATHS.

Five main afferent paths terminating in the cortex are recognized; four of these have been identified with virtual certainty throughout their length, *i. e.*, the paths of *body sense*, of *sight*, of *hearing* and of *smell*. The path for *taste* is imperfectly known.

Under the designation *body senses* are included hunger, thirst, pain, warmth, cold, touch and muscle sense, the latter applying to the group of sensations aroused by stimulation of proprioceptors (page 502).

Points of Entry of Different Paths.—Receptive neurons from the receptors of body sense in skin and muscles of trunk and limbs, enter the cord by the dorsal spinal roots; from receptors of hunger, thirst and visceral pain, entry is to the brain stem by way of the tenth cranial (vagus) nerves; from the body-sense receptors in the head the path is over the sensory portions of the fifth (trigeminal), seventh (facial), ninth (glossopharyngeal) and vestibular branches of the eighth (acoustic) cranial nerves (the latter convey the important group of proprioceptive impulses from the non-acoustic labyrinth; page 504). The paths of sight are in the second (optic) cranial nerves; of hearing in the cochlear branches of the eighth; of smell in the first (olfactory); of taste in the seventh and ninth (page 709). The relations of these cranial nerves to the brain itself are indicated in Fig. 121.

Spinal Cord Afferent Tracts.—Receptive axons upon entry into the spinal cord divide, sending one branch posteriorly in the fasciculus interfascicularis (comma tract) and one anteriorly in the fasciculus cuneatus (Fig. 122). Both branches give off *collaterals*

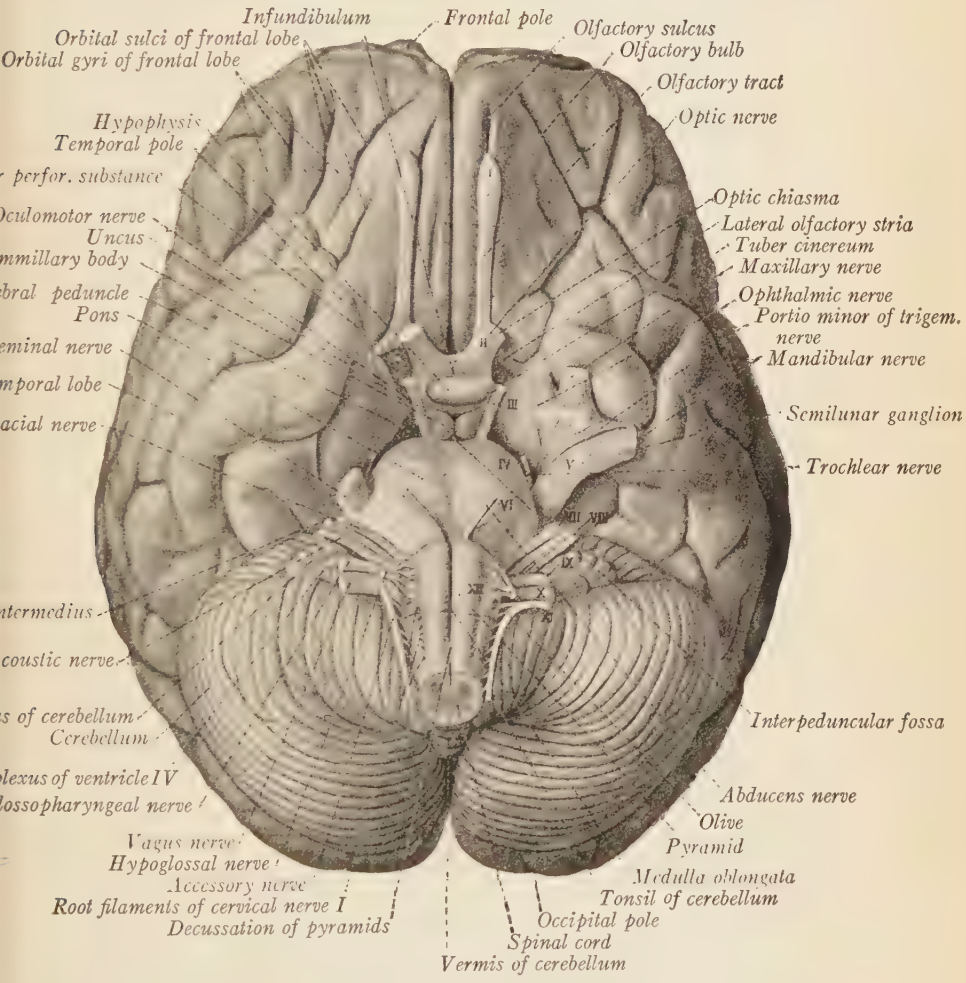

FIG. 121.—Ventral view of the human brain. (Sobotta-McMurrich.) (Ranson's Anatomy of the Nervous System, W. B. Saunders Company, Publishers.)

which penetrate the gray matter of the cord and make synaptic connection with neurons there. The latter may be either motor or internuncial. They afford the anatomical basis for spinal cord reflexes (page 120). The descending branch of the receptive axon

also terminates in the gray matter, forming the same sort of connection as the collaterals.

The ascending branch may terminate almost immediately, within the spinal cord segment it enters, in fact, or may extend anteriorly a greater or less distance. Fairly satisfactory evidence indicates that *proprioceptive* axons, *i. e.*, axons mediating muscle sense, extend the entire length of the cord in the dorsal funiculi to terminations in the nucleus gracilis or nucleus cuneatus in the medulla (Fig. 123). Those terminating in the gracile nucleus come from the posterior part of the cord (sacral, lumbar and inferior thoracic), being crowded toward the mid-line as they pass forward by the entry of new axons into the funiculus cuneatus from dorsal roots further forward.

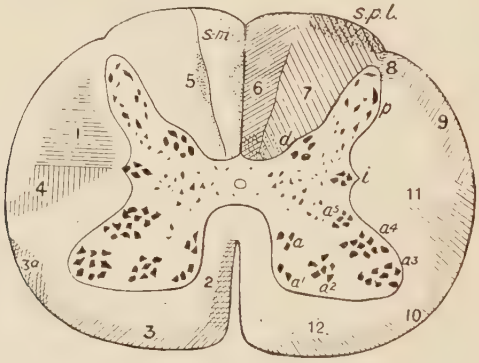

Fig. 122.—Diagram showing the location of the principal fiber tracts in the human spinal cord. Ascending tracts on the right side; descending tracts on the left. 1, lateral corticospinal (crossed pyramidal) tract; 2, ventral corticospinal (direct pyramidal) tract; 3, vestibuli spinal tract; 4, rubrospinal tract; 5, fasciculus interfascicularis (comma tract); 6, fasciculus gracilis; 7, fasciculus cuneatus; 9, fasciculus cerebellospinalis (Flechsig); 10, fasciculus anterolateralis superficialis (Gower); 11, lateral spinothalamic; 12, ventral spinothalamic. (From Schäfer's Essentials of Histology, by permission of the author.)

Collaterals from these proprioceptive axons terminate in the dorsal horns of gray matter in sympathetic connection with cells that give rise to the *cerebellar fasciculi* (Fig. 123). Two of these are present in each half of the cord; the *cerebello-spinal fasciculi* (tracts of Flechsig) are composed of internuncial axons from cell bodies on the *same side* of the cord (Clarke's column), hence convey to each half of the cerebellum proprioceptive impulses from its own side of the body. Each *fasciculus antero-lateralis superficialis* (Gower's tract) arises chiefly from cell bodies on the *opposite side* of the cord and, therefore, conveys to either half of the cerebellum proprioceptive impulses from the opposite side of the body. The cerebello-spinal fasciculi enter the cerebellum by way of the inferior peduncles (restiform bodies) the antero-lateral fasciculi extend

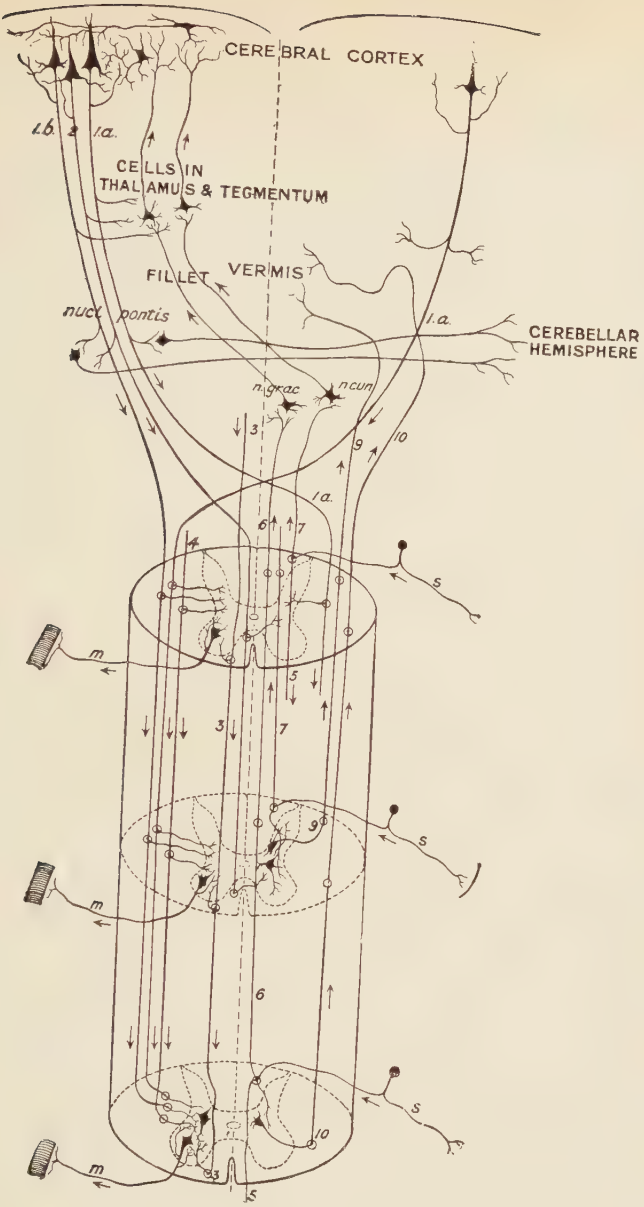

FIG. 123.—Diagram showing the course of the fibers in the main tracts of the spinal cord (Schäfer). 1*a* and 1*b*, pyramidal fibers (efferent) passing to the lateral corticospinal tracts of the opposite and same sides respectively; 2, pyramidal fiber to the ventral corticospinal tract; 5, descending branch of a receptive neuron (*S*) in the fasciculus interfascicularis; 6, ascending branch of a receptive neuron (proprioceptive) in the fasciculus gracilis; 7, similar fibers in the fasciculus cuneatus; 9, an internuncial afferent fiber (proprioceptive) in the fasciculus cerebellospinalis; 10, a similar fiber in the fasciculus anterolateralis superficialis; *n grac.* and *n. cun*, cells of the nuclei gracilis and cuneatus respectively. (From Schäfer's Essentials of Histology, by permission of the author.)

through bulb, mid-brain and pons to enter the cerebellum by way of the superior peduncles.

The ascending branches of axons from receptors of *pressure* (page 520) terminate within the same or a neighboring spinal cord segment in the dorsal horn of gray matter, whence second-rank neurons extend across the cord in the ventral white commissure. An afferent tract in the ventral funiculus is looked upon as the site of these second-rank axons as they pass forward in the cord (Fig. 124). Many of the axons composing this tract are short, extending only a few segments up the cord, to turn again into the gray matter where connection is formed with neurons of the next rank, whose axons extend the tract a few segments further, to terminate similarly. The tract as a whole ends in gray matter of the bulb.

The ascending branches of the axons which mediate the other body senses (*i. e.*, pain, warmth and cold) follow a course similar to that followed by the pressure mediating axons, but the tract by which the second rank and succeeding short axons ascend the cord is thought to be in the lateral funiculi, quite distinct from the tract by which the pressure mediating axons ascend.

The above account of the afferent tracts of the cord is summarized graphically in Fig. 124 and verbally as follows: Proprioceptive impulses destined for the cerebrum ascend by homolateral "long tracts" in the dorsal funiculi; those destined for the cerebellum by homolateral (cerebello-spinal) and heterolateral (superficial anterolateral) tracts in the lateral funiculi; pressure impulses ascend by heterolateral "short tracts" in the ventral funiculi; impulses of the other body senses ascend by heterolateral "short tracts" in the lateral funiculi. The evidence on which the above distribution is based is partly experimental, obtained by observing the after effects of sections of given funiculi in experimental animals, and partly clinical, obtained by study of patients with spinal cord lesions. Evidence from experimental animals must be applied to man with caution, since there is reason to believe the functions performed in lower mammals by "short tracts," *i. e.*, tracts connecting one cord segment with the next or a neighboring segment, to be taken over more or less fully in man by "long tracts" extending the length of the cord. This is in line with the conception that the brain becomes increasingly dominant over the cord as the animal scale is ascended, reaching maximal dominance in man. The dorsal funiculi are the most conspicuous long tracts not destined for the cerebellum, and the idea just expressed would tend to place the burden of conveying all impulses of body sense more heavily on them and less heavily on afferent tracts of the lateral and ventral funiculi in man than in the lower animals.

Afferent Tracts in the Brain Stem.—The nuclei of the fasciculus gracilis and fasciculus cuneatus contain the bulbar terminations

of the axons traversing the corresponding cord regions (Fig. 123). It is generally assumed that the axons which complete the "short tracts" in ventral and lateral funiculi terminate in the same nuclei, or in closely adjacent nuclei of the bulb. All impulses of body sense are thus thought to pass from spinal cord neurons to brain neurons in a relatively restricted area. The path is carried forward through the brain stem by a well-marked tract which at the beginning consists of the internal arcuate fibers. These cross the mid-line at the "sensory decussation" and continue forward as the *lemniscus* (median fillet). Afferent fibers from body sense receptors in the head join themselves to the lemniscus along its course.

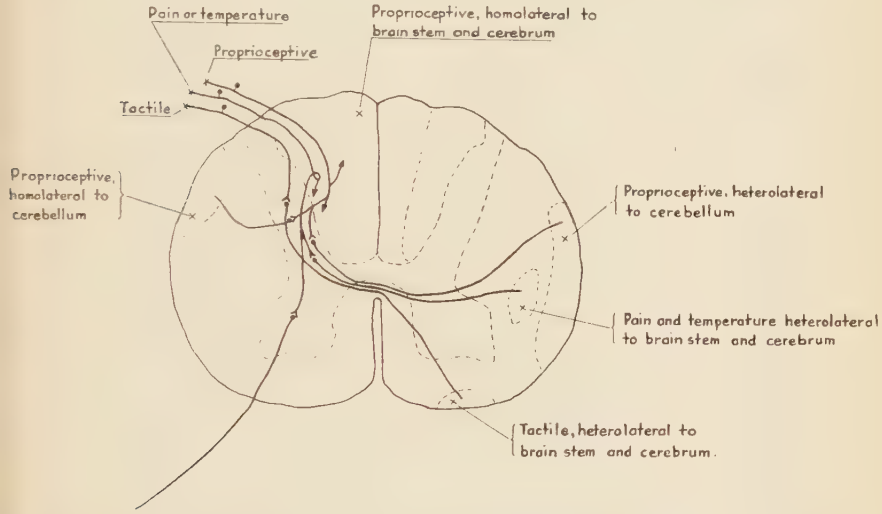
Pain or temperature
Proprioceptive, homolateral to brain stem and cerebrum
Proprioceptive
Tactile
Proprioceptive, homolateral to cerebellum
Proprioceptive, heterolateral to cerebellum
Pain and temperature heterolateral to brain stem and cerebrum
Tactile, heterolateral to brain stem and cerebrum.

FIG. 124.—Diagram illustrating the paths in the spinal cord of the three main body-sense neuron groups. (Adapted from W. Page May.)

It should be noted that the effect of the crossing described above is to bring proprioceptors of one side of the body into communication with the brain of the opposite side. Whether the connection of the other body sense receptors is also crossed is less certain. If their spinal cord path in man is mainly by the dorsal funiculi, as suggested above, their brain connections are the same as of the proprioceptors. The connections of the "short tracts" appear, however, to be with the brain of the same side, since they are thought to cross the mid-line in the cord (Fig. 124), and to cross back again in the sensory decussation in the bulb; any body senses that follow the latter path are, therefore, ultimately homolateral. The termination of the lemniscal axons is mainly in the thalami, although some are distributed to the superior colliculi.

The second afferent tract known in detail is that over which visual impulses pass. The course is from the retinæ over the optic nerves to the *optic chiasma;* thence by the optic tracts to the lateral geniculates mainly; also in part to the thalami and superior colliculi. A significant fact is that the decussation at the chiasma is not complete; the right optic tract is composed of axons from the right halves of both retinæ and the left tract of axons from the left halves of both (Fig. 125). Axons from each fovea are distributed to both optic tracts. The effect of this arrangement is that, while section of either *optic nerve* results in total blindness of the corresponding eye, section of either *optic tract* results in half blindness (hemianopia) in both eyes, localized on the corresponding halves of the retinæ, and not involving either fovea.

The third well-known afferent tract is that of hearing (Fig. 126).

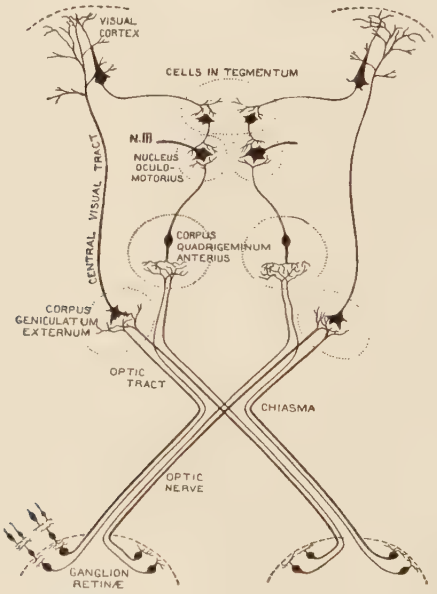

Fig. 125.—Diagram showing the course and chief relations of the afferent tracts for visual impulses. (From Schäfer's Essentials of Histology by permission of the author.)

The cochlear branch of the eighth cranial nerve connects with receptors in the acoustic labyrinth and is, therefore, to be regarded as the acoustic nerve proper. This nerve enters the pons where part of its fibers terminate in the *accessory nucleus* (ventral nucleus) and part in the *tuberculum acousticum* (dorsal nucleus). From these nuclei the pathway crosses the mid-line, partly as the corpus trapezoideum and partly in the auditory striæ, visible in the floor of the

fourth ventricle. Thence the path continues forward as a well-marked tract, the *lateral lemniscus*, to terminations in the inferior colliculi, the internal geniculates and the superior lemniscal nuclei.

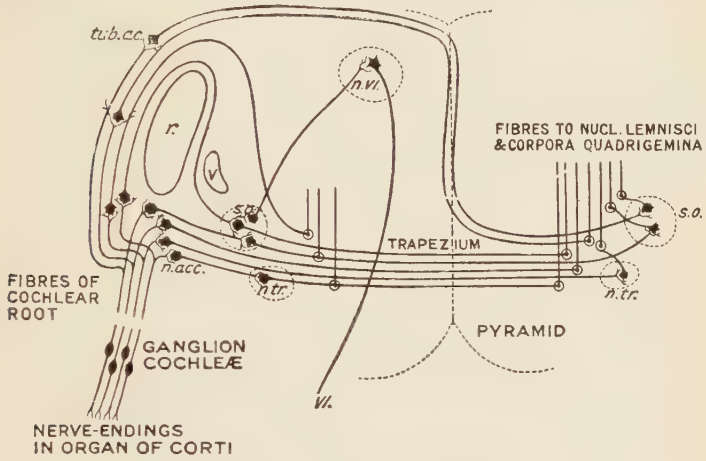

FIG. 126.—Diagram showing the course and connections of the afferent path for auditory impulses, *n. acc.*, accessory nucleus; *tub. ac.*, tuberculum acousticum; the "auditory striæ" are at the upper margin of the diagram. (From Schäfer's Essentials of Histology by permission of the author.)

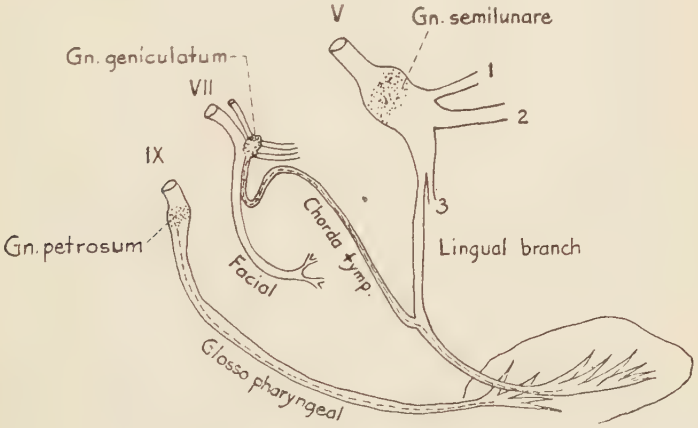

FIG. 127.—Diagram showing afferent paths for taste impulses from tongue to brain (adapted from Cushing). Dotted lines indicate course of taste fibers.

Some evidence indicates the crossing not to be complete, part of the axons from the pontine nuclei possibly passing to the lemniscus of the same side.

Afferent neurons from the receptors of taste (Fig. 127) have been

traced as far as the brain; dendrons from the anterior two-thirds of the tongue pass by way of the lingual branch of the fifth to the chorda tympani, over which they pass to the facial nerve, to cell bodies in the geniculate ganglion; dendrons from the posterior third extend in the glossopharyngeal nerve to the ganglion petrosum; receptive axons pass from these ganglia into the brain, but their further course within the brain stem is unknown.

Receptive neurons from the organ of smell pass directly to the *olfactory bulbs*, which are cerebral outgrowths. The sense of smell is, therefore, unique in that its afferent pathway does not traverse the brain stem. The connections of the olfactory bulbs with the brain are by means of the *olfactory tracts* (Fig. 128). The neurons composing these tracts terminate in nuclei in the base of the cerebrum (the so-called *olfactory area*).

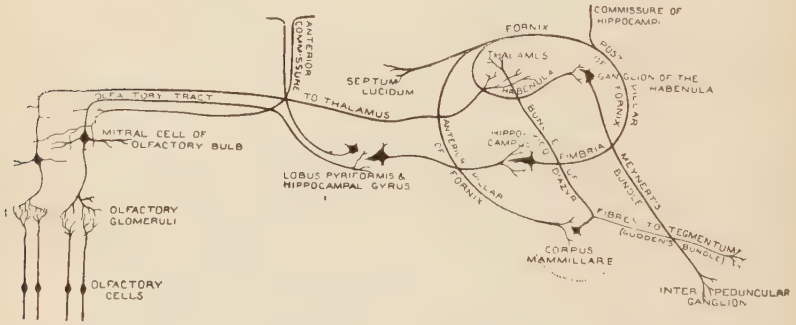

FIG. 128.—Diagram of the olfactory path. (From Schäfer's Essentials of Histology by permission of the author.)

A significant fact brought out in the above paragraphs is that all the afferent paths whose courses are known (and by inference the path of taste as well) have axon terminations in nuclei located either in the base of the cerebrum or in adjacent regions of the mid-brain. The effect is to subject this relatively restricted area to bombardment by afferent impulses from the entire receptive mechanism. Certain types of reflexes, chiefly cardiac (page 304), vasomotor (page 334) and respiratory (page 381), which appear to depend on mass afferent stimulation rather than on localized stimulation from specific receptors, are thus provided for.

SENSORY AREAS OF THE CORTEX.

Each sensory tract extends forward from its mid-brain termination in thalami, geniculate bodies, colliculi, olfactory nuclei, or adjacent structures by a group of neurons whose cell bodies are in

one or other of these nuclei and whose axons pass as units of the *corona radiata* (Fig. 119) to a definite area of the cerebral cortex. The *body sense* areas are in the postcentral gyri, immediately behind the central sulcus. There is some evidence that impulses from the legs pass to the uppermost portions of the areas; those from the arms, to portions lower down; and those from the head, to the undermost portions (von Frey). To the body sense areas pass all impulses that reach the cortex by way of the medial lemnisci. Since the lemniscal path itself terminates in the thalami and adjacent nuclei, it is conceivable that not all body sense impulses pass on to the cortex. Thus, some investigators have suggested the possibility that sensations of pain, or, at least of some types of pain, may be mediated by the thalami; the basis for this suggestion is the observation that electrical stimulation of the body sense areas of the cortex in human patients in whom the area has been exposed by trephine operation does not result in painful sensations, although sensations referable to other body senses have been observed. On the other hand, subjective pain is experienced by some patients with thalamic lesions, when no peripheral painful stimulation can be demonstrated. It is fairly clear, in any event, that touch, warmth, cold, such muscle sense as rises to the level of actual sensation, and presumably hunger and thirst, impinge on the cortex in the body sense areas.

The sensory areas for vision are located in the occipital lobes. Axons arising from cell bodies in the nuclei in which the mid-brain visual tracts terminate (page 708) pass by a section of the corona radiata (*D*, Fig. 119) to the occipital cortex. Unilateral destruction of the latter has the same effect *in consciousness* as transection of a single optic tract, *i. e.*, hemianopia. The total effect of the two lesions is not the same, however, since transection of a tract abolishes certain visual reflexes, mediated through the mid-brain nuclei, which reflexes persist after injury to the occipital cortex.

The sensory areas for hearing are in the temporal lobes, apparently mainly in the superior temporal gyri. Here are the terminations of axons springing from the mid-brain nuclei in which the fibers of the lateral lemniscus terminate (*E*, Fig. 119).

The sensory areas for taste are thought to be in the hippocampal gyri, although the evidence for this location is scanty and not specially satisfactory.

The sensory areas for smell have been quite satisfactorily shown to be also in the hippocampal gyri (uncinate portion). Axons from the basal olfactory area (page 710) pass directly to these gyri. In man, with his comparatively rudimentary smell sense, the central nervous structures concerned in olfaction are much less highly developed than in forms, like the dog, in which smell is a factor of prime importance in determining behavior.

EFFERENT TRACTS FROM THE CORTEX.

The main efferent tracts from the cortex are the *pyramidal,* or *cortico-spinal tracts* (*B,* Fig. 119). The axons of which these tracts are composed arise from characteristic cell bodies (giant pyramidal cells) in the precentral gyrus and contiguous areas of the first, second and third frontal gyri in each hemisphere. The cortical region from which these axons spring is known as the *motor area.* Each pyramidal tract begins as a section of the corona radiata, converging upon the *internal capsule,* a narrow space between the basal nuclei into which all projection fibers are crowded, both efferent and afferent, save those originating in the basal nuclei themselves. Below the internal capsule the pyramidal tracts from the two hemispheres emerge as well-marked bundles of axons (anterior pyramids) on the ventral aspect of the bulb. Not all the axons extend this far; many terminate in the pons (first crossing the mid-line), in synaptic connection with efferent (motor) neurons of the cranial nerves.

The main portion of each pyramidal tract crosses the mid-line near the lower end of the bulb, the *decussation of the pyramids* being thus formed. Beyond the decussation the crossed pyramidal tracts continue down the cord in the lateral funiculi (Fig. 122). Not all the axons cross over at the decussation. The residue continue down the ventral funiculi of the cord on the same side, constituting the *direct pyramidal tracts* (Fig. 122); some axons of these tracts cross the cord at intervals in the ventral white commissure; consequently the majority of pyramidal axons terminate on the opposite side of the body from that in which they originate. The physiological effect of this arrangement, which is that the left half of the cerebrum controls the right side of the body, and *vice versa,* has long been known, since unilateral paralysis of cortical origin (hemiplegia) was discovered early in medical history to be due to a heterolateral brain lesion. The crossed control is not absolutely complete; some muscles, notably those of respiration (page 365) appear to receive cortical innervation from both motor areas.

All pyramidal fibers, so far as can be determined, end in synaptic connection with somatic motor neurons, which connect, in turn, with skeletal muscle fibers. Thus communication between the cortex and the most remote muscles is over a path consisting of but two neurons.

An interesting anatomical fact is that the order of arrangement of the pyramidal neurons in the cortical motor areas of apes and man is the same as of the cranial and spinal nuclei to which the axons are distributed in brain stem and cord; the sequence is reversed, however, the cortical area for the cranial nerves being in the lower portion of the motor cortex and the areas for the spinal nerves

extending in succession toward and into the mesial sulcus (Fig. 129). This distribution has been demonstrated experimentally by electrical excitation of the cortex in apes (Sherrington) and in patients in whom the motor area has been exposed by trephine operation. By using carefully localized electric shocks, applied in order to different regions of the motor area, beginning at its lower margin, the various muscle groups can be thrown into contraction in the succession shown in Fig. 129. Incidentally it should be noted that such excitation in fully conscious human patients is not attended by painful sensations, nor for that matter by any direct sensations

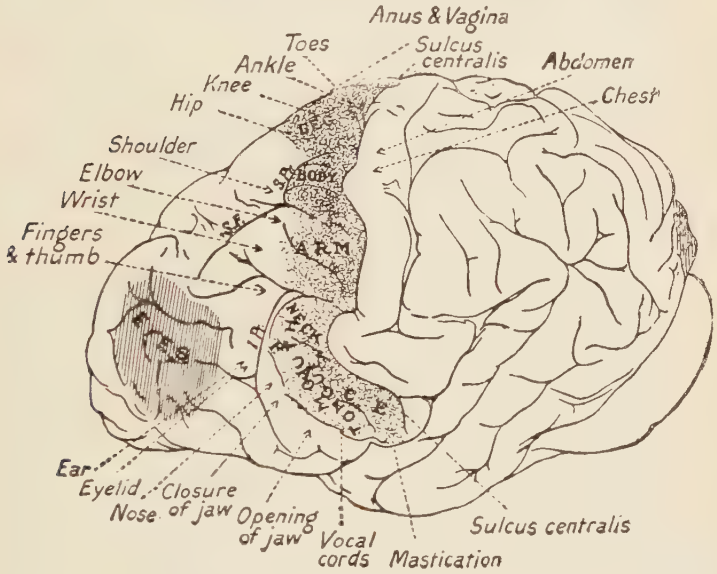

FIG. 129.—Outer surface of brain of chimpanzee, showing localization within motor cortex (Sherrington). (Starling's Physiology, Lea & Febiger.)

whatever, although the muscular contractions evoked by the stimulation give rise to the usual sensations of muscle sense, perceived by the patient in the normal manner.

Another well-marked efferent tract from the cortex is from the frontal lobe to the pons, and thence to the cerebellum (*A*, Fig. 119). This tract, known as the frontal cerebro-cortico-pontal tract, is to be looked on as the path by which impulses from the cerebrum may be brought to bear on the cerebellum, presumably to play a part in arousing the fine control exerted by the latter organ over complex muscular movements. It is probable that the same tract conveys also the impulses by which the reactions evoked without volition by certain affective states are mediated (page 735).

SIGNIFICANCE OF ASSOCIATION AND COMMISSURAL FIBERS.

The projection fibers provide for the impingement of impulses of exogenous origin upon the cortex and for the outward flow of impulses by which the cortex brings influences to bear on the body. The machinery by which the primary cortical function, the exercise of choice (page 699) is mediated, involves also the existence of abundant intercommunications among the cortical neurons themselves. It is obvious that choice to be serviceable must be based on information gained through receptor stimulation. Impulses evoked thus impinge on the cerebrum only in the sensory areas. From these areas impulses must pass, either directly or indirectly (see Chapter XXXIX), to the motor areas to serve as the basis for the discharges from these areas by which the reactions of choice are actually carried out. The association fibers provide the necessary means of communication between one area of the cortex and another. The successful exercise of choice implies much more, as will be seen in Chapter XXXIX, than the passage of impulses from sensory to motor areas; large additional areas are also involved. Intercommunications among all these are provided for by association fibers. These are additional to abundant intercommunications among immediately contiguous cortical neurons. Apparently only the more distant connections depend on association fibers.

The two hemispheres of the cerebrum function in complete harmony under all normal conditions, as instanced by the perfection with which bilateral movements of arms or legs may be synchronized. It is, in fact, much more difficult to perform non-related actions of opposite arms or legs than related. This harmony is undoubtedly maintained by the passage of impulses over the commissural fibers, although practically nothing is known as to the details of the mechanism by which commissural impulses operate to produce the harmonious results secured.

Summary.

The presence of *distance receptors* permits reactions to be delayed and yet be serviceable to the organism. Thus, selective reactivity or *choice* enters as a factor by which reflexes may be modified.

The great development of the anterior ganglia of the nervous system into a *brain* is considered to be related to the presence of the complex distance receptors at the anterior end of the body, involving, of necessity, an exceptional wealth of synaptic junctions within the adjacent regions of the central nervous system.

The machinery of selective reactivity is considered to reside in the *cerebral* cortex, a region containing enormous numbers of inter-

nuncial neurons, characterized by particularly rich synaptic interconnections. The latter are proportionally more numerous in man than in any other organism—a fact presumably important in explaining man's superior intellectual capacity.

The cerebral white matter underlying the cortex consists of myelinated axons, which fall into three categories: (*a*) *Projection* fibers, connecting the cortex with other parts of the nervous system; (*b*) *association* fibers, connecting homolateral cortical areas; (*c*) *commissural* fibers, connecting heterolateral cortical areas.

Projection fibers are *afferent* or *efferent*. Under the former head come the final ranks of neurons in the nerve paths between the receptors and the brain; the latter head includes the first neuron rank in the path from cortex to effectors.

Five main afferent paths to the cortex are recognized, viz: of *body sense*, of *sight*, of *hearing*, of *smell* and of *taste*. The first four have been worked out with practical completeness; the fifth is imperfectly known.

Ascending paths are present in the spinal cord in the dorsal funiculi and in areas of the ventral and lateral funiculi. The first are "long tracts" and homolateral. They are identified as proprioceptive, although some evidence indicates that in man they may convey impulses from other receptors as well. The ventral and lateral ascending tracts are "short" and heterolateral; the first is identified with touch, the second with the remaining body senses. All terminate in the nuclei of the fasciculus gracilis or fasciculus cuneatus, or in closely adjacent nuclei.

Cerebellar tracts are present in the margins of the lateral funiculi; the cerebello-spinal is homolateral; the superficial antero-lateral is heterolateral.

The tracts of *body sense* pass through the brain stem in the median *lemnisci*. These cross the mid-line in the sensory decussation; they terminate mainly in the thalami; in part in the superior colliculi.

The paths of *vision* are over the optic nerves to the optic chiasma, where half-crossing occurs, the paths continuing in the optic tracts. Both foveæ are represented in each tract. The tracts connect with the lateral geniculates, the superior colliculi and the thalami.

The tracts of *hearing* extend by way of the cochlear branches of the eighth nerves to pontine nuclei; thence cross the mid-line to extend forward in the lateral lemnisci to terminations in inferior colliculi, internal geniculates and superior lemniscal nuclei.

The tracts of *smell* pass to the olfactory bulbs; thence to olfactory nuclei in the base of the brain, making up the *olfactory area*.

The fact that all afferent tracts have terminations in mid-brain or cerebral basal nuclei is considered significant in the mediation of such reflexes as cardiac, vasomotor and respiratory.

From the mid-brain and cerebral nuclei the various sensory tracts extend by way of the corona radiata to definite cortical areas. The areas of body sense are in the postcentral gyri; of vision in the occipital lobes; of hearing in the temporal lobes (superior temporal gyri); of taste, probably in the hippocampal gyri; of smell in the same (uncinate portion).

The main *efferent* cortical tracts are the *pyramidal* (cerebrospinal). These traverse the bulb as the anterior pyramids, crossing the mid-line (in part only) at the decussation of the pyramids. The continuation of the crossed fibers down the cord is in the lateral funiculi (crossed pyramidal tracts); of the uncrossed fibers in the ventral funiculi (direct pyramidal tracts). The major portion of the latter ultimately cross the mid-line within the cord.

The pyramidal tracts originate in the *motor areas* of the cortex in the precentral gyri. The pyramidal axons end in immediate synaptic connections with somatic motor neurons, thus providing the mechanism for volitional control of the skeletal muscles.

An additional efferent tract (frontal cerebro-cortico-pontal) connects the frontal cortex with the pons and indirectly with the cerebellum. This tract is presumed to mediate such relationship as the cerebrum has with cerebellar function. Conceivably other non-volitional efferent impulses pass over the same tract.

The *association* fibers are presumed to furnish the pathways (direct or indirect) from the sensory to the motor areas, over which the impulses pass by which selective reactivity is mediated. This function is so complex as to involve much or all of the cortex; hence, association fibers occur connecting all cortical areas with one another.

The *commissural* fibers convey the impulses by which the two cerebral hemispheres are caused to function harmoniously in evoking or controlling bodily reactions.

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CHAPTER XXXIX.

CEREBRAL FUNCTION: ACQUIRED REACTIONS; CONDITIONED REFLEXES; AUTOMATISMS.

Introspection a Method of Studying Cerebral Function.—Any attempt to picture in detail the functioning of the human cerebrum must take into account, at the outset, the important fact that this organ is unique in that we can study it not only by the ordinary objective methods available in all fields of investigation, but also subjectively, by *introspection*. The latter method is of limited application in physiology, yet cannot be disregarded altogether if anything like an adequate conception of cerebral function is to be had. The justification for interpreting data obtained by introspection, as applicable to the cerebrum and it only, is of necessity inferential rather than strictly experimental. It should be stated, however, that such objective evidence as we have points definitely to the conclusion that the processes by which introspection is mediated, *i. e.*, attention and reflection, cannot function except through the agency of the cerebral cortex.

MIND CONSIDERED FROM THE VIEWPOINT OF PHYSIOLOGY.

It is customary, as well as scientifically permissible, to use the term *mind* to cover the sum total of cerebral processes. So far as these processes can be explored by introspection they make up the "conscious mind;" they necessarily involve the cortex. Other cerebral processes, not susceptible to this means of approach, also occur. These make up the "subconscious mind." It is conceivable, though neither proved nor disproved, that subcortical centers of the cerebrum may mediate subconscious mentality to some extent.

From the viewpoint of biology, that is to say, considered as a factor in behavior, the mind may be defined as the central mechanism for selective reactivity, in other words, for the exercise of choice (page 699). Only as the mind functions to this end does its study come within the scope of physiology; the ensuing elementary discussion of mind is organized, therefore, in accord with the above definition.

MEMORY.

The first essential to the exercise of choice is a means whereby delay in the completion of reflexes can be brought about. In the description of the operation of the nervous system in Chapter VIII

impulses are pictured as passing from neuron to neuron, with no more loss of time than is actually required for making the passage, so that a reflex action once started proceeds to its end within a brief time, usually a small fraction of a second. The cortex of the cerebrum differs from other parts of the central nervous system in that it has the property of causing a separation in time of incoming, *i. e.*, afferent, impulse streams from the efferent or outgoing streams to which they would naturally give rise. Note that this is not a simple blocking of the afferent impulse streams through synaptic resistance too high to be overcome, and so an extinguishment of the nervous activity in toto, but a retention within the cortex of a state due to the nervous activity, in readiness for later release. This retention is the physiological basis of memory. How it is achieved is not known. Significant facts are that individual memories may persist throughout life, and that they may serve repeatedly to play a role in influencing behavior.

Experience the Basis of Choice.—The importance of memory in connection with the exercise of choice is obviously that choice to be serviceable to the organism must have a definite basis. There is no advantage in random choosing. The only possible basis for successful choice is previous experience on the part of the organism itself. We may suppose that an animal upon being first confronted with a given situation makes a response at random. If this random reaction is extreme in its non-adjustive character the animal will be destroyed, if the response falls short of this fatal outcome, and the organism survives, or if it proves distinctly advantageous, there will clearly be a gain when next the same situation confronts the animal if the former experience can be drawn upon to aid in determining the present response. Previous experience cannot be drawn upon unless registered in some utilizable form within the nervous system. Given an arrangement whereby every experience sets up a memory, and a further arrangement to make this memory accessible for use whenever needed, we have the rudiments of a means for enabling organisms to profit by their past experiences.

Sensory Areas in Relation to Memory.—The term experience as used above covers both the purely sensory impressions an organism receives and the reactions it performs in response to them. There is no doubt that both classes of experience are registered in memory. Sensory impressions impinge first upon the cortex in one or another sensory area (page 710). The presumption is that the primary memories of such impressions are registered in or near their respective sensory areas.

Percepts.—By introspection of sensory impressions as received and as remembered we learn that the mind does not deal with sense impressions as such, but with judgments or interpretations based on them, which we designate as *percepts* (page 482). The sig-

nificance of this fact in physiology is that not pure sensory impressions but percepts derived from them form the basis both of memory and of choice. The sensory impression is determined in part by the environmental situation by which it is evoked and in part by the physiological state of the receptor (page 486); the percept, on the other hand, is modified through mental processes, so that what we *perceive* is not necessarily the same as what we *see*. To illustrate: If one looks about a room he sees angles on every side, either in the corners of the room itself, on windows and doors, or on articles of furniture. These angles are rarely *seen* as right angles, but are always *perceived* as such. In other words, they register in the mind in the latter form. Similarly, one may handle a book in the dark; the actual sensory impressions are of certain shapes and textures, of a given size and weight; the perception is of a definite object, *i. e.*, a book.

Sensory Illusion.—It is probable that percept formation is a necessary step in the utilization of sensory impressions in the exercise of choice. From the statements in the last paragraph it follows, however, that to the extent that percepts depart from actual fact they may lead to wrong choices. A familiar illustration of a percept not in accord with fact (in other words, a *sensory illusion*) is the over-estimation of vertical heights. If anyone is asked to open a window until the opening is perceived as square, and then to measure the sides of the opening, he is sure to find the vertical sides shorter than the horizontal. Obviously a workman who should undertake to construct a series of square windows, using his perception of squareness as the only guide, would waste both his materials and his labor.

Associative Memory.—The significance of memory is, as already stated, that it makes previous experience available as a basis of present behavior. The organism incurs very many experiences in the course of its normal life. In any given situation the more fully these are utilized in making choice among alternative reactions the more advantageous is the adjustment likely to be. The utilization of the whole background of experience implies the presence in the cortex of a means for grouping together such experiences as are related. This means exists in man and in a wide variety of lower animals, although apparently not present in insects, notwithstanding the high degree of nervous organization these forms possess. It is known as "associative memory," and is defined as the bringing together of related percept memories to form a new group-percept, sometimes distinguished by the designation *concept*.

A standard illustration is the experience of the infant with a bell. He may see the object and remember its appearance; he may hear and remember its sound; finally he may handle it and establish memories of its tactile qualities. If his mental processes were to

go no further he would have, presumably in three distinct cortical areas, memories applying to one and the same object. These related memories actually become merged, however, into a single percept of "bell," which is henceforward retained as a definite memory in its turn. The process of merging is pictured as the passage of nerve impulses over associative (or commissural) fibers of the cortex from the areas where the primary memories are registered to a common meeting point in some one of the cortical areas not concerned primarily with the receipt of afferent or the discharge of efferent impulses. These areas include the major part of the frontal and parietal lobes, the whole of the islands of Reil and considerable portions of the temporal and occipital lobes. They are known as *association areas* to signalize their postulated function as the seat of associative memory.

The thought process consists largely of the building together into new concepts of material present as memories; or of building new material as received in the form of current experience into concepts previously formed, thus enlarging and enriching them. The properties of *reflection* and *attention* are concerned in this process; but as to how they operate we know nothing.

EFFECTS OF DECORTICATION.

In most vertebrate species up to and including the dog the entire cerebral cortex can be removed or destroyed experimentally, provided injury to lower nervous structures has been avoided, without harm to the machinery by which most automatic reflexes are carried on. A decorticated pigeon, rat, rabbit or dog conducts itself in the main very much as does a normal individual of the same species. However, its activities reveal a striking absence of ability to profit by previous experience; no such traits as judgment or discrimination can be detected. Furthermore, all *volitional* activities are wanting, as are all manifestations indicative of what we know in ourselves as *consciousness* (page 731). The organism may be, nevertheless, a fairly efficient automaton, performing complex acts successfully, including locomotion and the swallowing of food placed in the mouth. These acts are performed, however, only under the impulsion of adequate *immediate* stimulation. A decorticated pigeon, if deprived of food, becomes restless, walking about continuously and pecking aimlessly at the gound or at objects thereon. When fed, the restlessness disappears. The inference is that hunger receptors (page 393) are stimulated when food is too long withheld, evoking in wholly automatic fashion reflexes of walking and pecking. Experiments of this character confirm very definitely the conception of the cortex as the seat of the mechanism for the exercise of choice.

ACQUIRED REACTIONS.

Learning.—Among the striking differences between a decorticated and a normal animal is the occurrence in the latter of reactions resembling ordinary reflexes in that they follow directly upon definite receptor stimulation, yet unlike such reflexes, in that they are obviously not due to the hereditary blocking out of definite reflex paths; they have come into existence, instead, as the result of experiences that have befallen the organism during its own lifetime. A method by which such *acquired reactions* are established is illustrated by an experiment frequently performed in laboratories devoted to the study of animal behavior. The experiment is in outline as follows:

A test animal is placed in such a situation that to escape from confinement or to obtain coveted food some specialized reaction, outside the scope of its ordinary behavior, is necessary. The situation is of a sort to impel the organism to action, in that the confinement is irksome, the animal is hungry, or the food is within sight or smell. The animal, therefore, becomes active, in more or less random fashion, and sooner or later blunders upon the particular reaction by which the cage is opened or the food made accessible. When the experiment is repeated the time spent in random activity is found to be shortened; the correct reaction is performed sooner than before. After a series of repetitions the random motions drop out altogether; the organism performs the correct reaction at once. The interpretation usually put upon this phenomenon is that all the motions, unsuccessful as well as successful, make their impression in memory on the cortex, but the successful become associated with the attainment of the desired result, and hence are the only ones to become built into a concept that is in course of gradual development through the operation of associative memory, and that will function in a manner indicated below to mediate the acquired reaction. When the concept has become thoroughly organized the "learning process" so far as the particular problem in hand is concerned is completed.

The Reasoning Faculty.—The process of learning is thus seen to consist in building up definite concepts through the operation of associative memory. Man, and to a limited extent some other of the higher mammals as well, may, however, escape more or less completely the necessity of arriving at correct responses by selection from a miscellaneous group of random actions. This possibility depends on the possession by these forms of the faculty of *reason*, a purely cortical faculty, which enables the organism possessing it to determine more or less successfully the correct reaction to a novel situation before any action whatever is undertaken. The concept by which the reaction is to be mediated is thus organ-

ized on the basis of material already at hand in the form of associative memories, with a minimum of assistance from external stimuli. To the extent to which this procedure is successful the learning process is abbreviated.

Concepts as Factors in Behavior.—However acquired reactions become established, whether by the slow and tedious method of "trial and error" or by the short-cut afforded by the reasoning faculty, they form the basis of "cortical behavior" in man and animals. The immediate cortical organization underlying any acquired reaction is, as stated above, a concept. The way in which concepts function to mediate reactions is pictured somewhat as follows: The acquired reaction is an adjustment to some particular situation; when this situation recurs it impresses receptors in a definite manner, arousing a characteristic stream of afferent impulses. These impinge on appropriate areas of the cortex, where they evoke their proper percepts (page 718). These at once interact with the concepts to which they are relevant, the interaction depending presumably on a flow of nervous impulses into the particular association areas of the cortex in which the concepts reside. Thence, either under the influence of volition, or under an emotional urgency (see Chapter XL) a further stream of impulses is caused to impinge on a definite area of the motor cortex. From the latter, in turn, proceeds a suitably coördinated discharge over pyramidal neurons to the effectors giving the appropriate reaction. Since the discharge from the association area is dependent on the action of a concept, it may be, and usually is, on a much larger scale than the afferent influx from the stimulated receptors. In other words, the impulse stream is built up during its passage through the association areas. Inasmuch as all concepts, no matter how elaborate are based ultimately on receptor stimulation one is justified in looking on such reactions as these as essentially *delayed reflexes.*

In an additional important respect already indicated (page 718) cortical reactions differ from reflexes as previously defined, *i. e.*, in that the concepts on which they are based are not obliterated by use. If we recur to the account of the typical simple reflex (page 120) it will be recalled that following the passage of the nerve impulse stream which mediates the reflex nearly complete restoration of equilibrium occurs, leaving the reflex arc in much the same state as though no reflex had been set up. Each simple reflex is thus, on the whole, a complete event. Concepts once established are, on the other hand, relatively permanent. Their participation in evoking one reaction does not lessen their capacity to participate in the evocation of others subsequently. This permanence of concepts is obviously fundamental to the machinery for utilizing previous experience, since without it no concept could serve to deter-

mine more than one reaction. As a matter of fact, the oftener a given concept or group of concepts is employed the more firmly does it appear to become established.

In another respect acquired reactions show a feature of difference from automatic reflexes, *i. e.*, in that while automatic reflexes are as a class predominantly due to stimulation of the category leading directly to *consummatory* reactions, in other words, are in most instances the result of stimulation of one or the other of the receptors listed in Chapter XXX, page 479, as tending to evoke prompt response, acquired reactions are quite commonly set off by stimulation of one or the other of the *anticipatory* receptors, *i. e.*, those acting at a distance, and hence enabling the organism to prepare its reaction before performing it.

UNCONDITIONED REFLEXES.

When the behavior of any higher organism is studied in detail much of it is seen to be made up of typical automatic reflexes. These, as already indicated (page 123) are *inherent* in the nervous structure of the organism, and hence are as characteristic of it as its anatomical features. An organism inherits a definite series of automatic reflexes just as truly as it inherits other ancestral traits. Since these inherent reflexes are not dependent for their existence on the circumstances in which the organism happens to be placed, they have been named *unconditioned* reflexes (Pavlov). They are easy to account for biologically, since they contribute directly to the well-being of the organism or the species; thus sneezing in human beings, scratching of an irritated skin area in dogs, the secretion of saliva when food is introduced into the mouth, are all unconditioned reflexes, and all serve or tend to serve useful functions in the economy of the organism.

CONDITIONED REFLEXES.

While the major part of the behavior of the higher organisms consists either of these inherent reflexes or of acquired reactions of the type described earlier (page 721), careful observation of such forms as dogs, cats, horses and especially human beings, reveals the more or less frequent occurrence of well-established activities, of a perfectly definite character, falling in a somewhat different category. The salient feature of these is that, while their *motor expression* is typical of some one or other of the inherent reflexes, the *sensory stimulation* by which they are evoked is not of the sort typically associated with the observed action. In other words, they are reflexes set off by other than their normal receptor stimulation.

The occurrence of such behavior as this has puzzled observers because it is often quite devoid of apparent biological significance. In this respect it contrasts strikingly with other activities of the organism, for most of which a definite biological basis is usually clear. An explanation of reactions of this kind has been provided through the researches of Pavlov. This investigator has demonstrated the conditions under which reactions whose motor expression is typical of inherent reflexes may come to be set off by other than their normal stimuli. Pavlov designates reactions of this class *conditioned reflexes* to emphasize their dependence on special conditions, and to distinguish them from unconditioned reflexes, in which the relation between stimulus and response is as inherent as the response itself.

The general nature of conditioned reflexes, and the way in which they come into existence, can be illustrated by an account of the experimental development of one of the simplest of them. In a normal intact animal (dog) an inherent reflex is evoked by application of its proper sensory stimulus. The secretion of saliva by placing food in the mouth is a particularly satisfactory reflex for the purpose. At the same time that the food stimulus is being applied, or just prior to its application, a second stimulus, neutral in effect on salivary secretion, such as the sounding of a certain musical note, is also brought to bear. This combination of a neutral with an effective stimulus is repeated several times (about thirty for maximal effect in dogs), whereupon the primary stimulus can be omitted, and the reflex elicited by simply sounding the correct note. An inherent response has thus been made subject to a previously neutral stimulus, establishing the relationship characteristic of conditioned reflexes.

The development *in the course of Nature* of a conditioned reflex nearly identical with the one just described is illustrated by the watering of the mouth when food is *seen* whether eaten or not. This latter relation has been proved not to exist inherently, nor is there any particular biological advantage perceptible in the preliminary secretion of saliva at the sight of food, although it occurs in many mammalian forms. In the life of almost any higher animal visual stimuli from the food ordinarily accompany or precede its ingestion. Thus, the combination of a neutral with an inherently effective stimulus is repeated frequently under natural conditions, with the inevitable result that a conditioned reflex is developed as described.

Any inherent reflex may serve, in theory, as the basis on which conditioned reflexes may be developed, and any "neutral" stimulus that can be practically brought to bear may be transformed into an effective stimulus for mediating a conditioned reflex. In the main, "anticipatory" stimuli from distance receptors fall into the "neutral"

category; consequently, most conditioned reflexes are based on anticipatory stimuli (page 481).

Cortical Function in Formation of Conditioned Reflexes. The physiological problem presented by conditioned reflexes is to account in terms of cortical function for the transformation of a neutral stimulus into an effective one. It is evident that by some associative process a stream of afferent impulses previously "neutral" is caused to impinge on a definite area of the motor cortex, causing the latter to discharge in typical fashion. In a previous paragraph (page 722) the basis for discharge of the motor cortex in an acquired reaction is pictured. The salient features of the action as there described are the merging of the immediate afferent impulse stream into the concept to which it is relevant and the subsequent discharge of impulses from the area in which the concept resides to the motor cortex, and thence to the proper effectors. The basis of the merging is *relevance*, the associative process acting to bring relevant impulses and memories together.

In the development of conditioned reflexes the essential relation is not of relevancy but of *time*. Two sense impressions, one inherently effective, the other neutral, impinging on the cortex in proper temporal relationship tend to become associated, after the general manner of concept formation. A single such temporal relationship does not suffice to establish a conditioned response, but does leave behind it a trace upon which a second occurrence of the same stimulus pair builds more strongly, thus with repetition the association becomes well established, and the neutral stimulus is transformed into an effective one. The factor of repetition is important in that it prevents random conjunction of two stimuli from setting up a conditioned reflex. Only when the conjunction is frequent does a reflex develop. It is also noteworthy that the neutral stimulus must not *follow* the inherent; it must accompany or precede it. As long an interval as thirty minutes may occur, although a conditioned reflex thus built up is less perfect in performance than when the two stimuli are nearly synchronous.

Elaboration of Conditioned Reflexes.—Although all primary conditioned reflexes depend on temporal association of neutral stimuli with inherently effective stimuli, secondary conditioned reflexes may be developed by relation with previously existent primary. For example, the secretion of saliva at *sight* of food is a primary conditioned reflex (see above). If an organism is *shown* food repeatedly, but not given any, at the same time as a note is sounded, reflex salivary secretion at the sound of the proper note is established in course of time, just as when the note is sounded in relation to placing food in the mouth. Similarly, after developing reflex secretion to the sound of a note this can serve as the basis for developing a tertiary conditioned reflex in response to some other neutral

stimulus. Since most organisms spend their lives in fairly uniform environments, in which much the same things happen over and over again, it is to be expected that in course of time elaborate series of conditioned reflexes may come into being, to play considerable parts in determining total behavior.

Persistence of Conditioned Reflexes.—By experiments on animals in which bizarre conditioned reflexes have been established, such as salivary secretion following the striking of a certain musical note, the fact has been brought out that occasional repetition (once every day or so) of the combination of stimuli to which the conditioned reflex is originally due is necessary to maintain it at full intensity. If the combination is not repeated, so that the conditioned stimulus is not brought again into association with the original stimulus the conditioned reflex gradually declines, and in course of time (perhaps several years) completely disappears. This fact illustrates strikingly the fundamental difference between conditioned and unconditioned reflexes. The latter are so deeply ingrained as not to be dislodged from their position as factors in behavior by any circumstances short of actual injury to the nervous structures by which they are mediated, while the hold of the former is so precarious that they may lapse through simple discontinuance of reinforcement.

Extinction of Conditioned Reflexes.—A further fact illustrative of the different hold on the nervous system of the two types of reflex is that a conditioned reflex may be extinguished by the simple procedure of repeating the conditioned stimulus over and over again in rapid sequence, without any inclusion of the inherently effective stimulus. The effect of this procedure, if the sequence is rapid enough, and the experiment continued long enough, is to dislodge the conditioned reflex completely, leaving the organism in the same state as before the reflex was developed. Extinction for a time, with spontaneous recovery, results from similar treatment not pushed to so great an extreme. Contrasted with this is the fact that inherent reflexes are not extinguishable, as pointed out above.

HABITS.

If acquired reactions are repeated often enough they come to be carried out, so far as the nervous system is concerned, in essentially the manner of ordinary reflexes. That is to say, the response follows the stimulus with the promptness and certitude characteristic of inherent reflexes. Furthermore, as every one knows from his own experience, *volition* drops out in course of time, the reaction, even though elaborate, coming to be mediated quite automatically. Reactions perfected to this extent are designated *automatisms*, or habits. An illustration is the tying of a cravat. When one first

learns to tie his cravat he gradually develops a typical acquired reaction. When, after long practice, he arrives at the point of finding himself in the morning with cravat correctly tied, without having been aware at any time of going through the tying process, the automatism may be said to be established.

LANGUAGE.

Among the auditory and visual stimuli significant as determinant factors in behavior none are more important to mankind than those making up spoken and written language. Language has two main functions: (*a*) As a means of direct communication among organisms; (*b*) as a vehicle for the *extension of experience* beyond the range otherwise possible to the individual. The first function calls for only brief comment. It is worthy of note that to a considerable extent *vocal communication* among organisms is independent of actual language, and is found in many lower forms, as well as in man. This type of communication is practically confined to biological fundamentals. A cry of fear, or anger, as when bodily harm threatens, an exclamation of delight at the discovery of food, the crooning of a mother over her young, are intelligible whether clothed in words or not, or if clothed in words, whether in a known tongue or not. Language proper does, however, increase the scope of direct communication, by making the imparted information explicit. One may thus learn not only that danger threatens, but its precise nature and extent. Not only may the presence of food be announced, but its palatability and quantity be made known as well.

The chief significance of language is, however, in its potentiality as a means of extending experience. Recalling that the primary function of the cerebral cortex is to make experience available as a factor in behavior, it is clear that the wider the background of experience the more successfully the cortex can function in determining the conduct of the organism. Man alone among organisms is able to incorporate into his mentality experiences he has not actually had or observed in person, because in him alone is the language function developed. Indeed, possession of the faculty of language and of a *mind good enough* to assimilate and utilize more or less successfully the vast mass of experience thus made available are the two attributes of the human species, susceptible of objective demonstration, on which the superiority of man over the lower animals is chiefly based.

Language may be defined as the adoption by mutual consent among a group of individuals of a series of arbitrary auditory and visual symbols to be associated with the various sense impressions, percepts, concepts and remembered motor expressions which together make up the content of mind. The symbols are themselves

pure sense impressions. In the child, or the adult for that matter, who is learning a language new to him, the basis of association is similar to that underlying conditioned reflexes. There is no inherent relation of relevancy in language associations, any more than in the association of conditioned stimuli with the reflex actions they evoke. In the process of learning a language there must be, however, definite *temporal* relationships between the hearing or seeing of words or sentences and the arousing in consciousness of the particular percepts or concepts into which they are to become incorporated. Furthermore, the element of repetition enters into language learning, as into the establishment of conditioned reflexes (page 724). The similarity between the two processes can be illustrated readily by citing experiences that might easily befall almost any infant. The signs of lively satisfaction displayed by the infant at the sight of mother or nurse bringing a bottle are conditioned reflexes, since the sight of milk in a bottle is obviously not an inherently effective stimulus to such reactions in infants. The child has experienced this stimulus frequently in temporal relationship with the satisfaction of its hunger, however, and so the reflex has become established. If the word "bottle" is spoken repeatedly in connection with the display of the bottle the infant soon learns to associate the auditory stimulus with the article; again under no other impulsion than a temporal relationship often repeated.

Language a Factor in Thinking.—A very significant fact about mental activity in man is that to a very large extent language serves as its vehicle. That is to say, in organizing simpler concepts into more elaborate (the essence of the process of thinking), the mind works with the words associated with the concepts, so that as these words are brought together in the new relationship the new concept forms in the mind. How vital this method is in the operation of the human mind is particularly well illustrated by mental processes in which abstractions are involved. The concept represented by the single word "language," for example, attains very great complexity in educated persons. The mind is able, however, in spite of the complexity of the concept to use it in developing a still more elaborate concept, say of "cortical function." The word "language" carries with it all necessary connotations, so that when the new concept is organized, and "cortical function" takes on its particular meaning, the significance of language as a factor is duly incorporated therein. The highest planes of human thinking are attainable only because mankind has this faculty of representing concepts in terms of words.

Language Areas.—*Aphasia.*—Although in man language is thus bound more or less intimately with the whole thought function, in other words, with the processes of associative memory in general, it is interesting to note that *impairment* of the language function

results from lesions in certain rather restricted portions of the cortical association areas, while other portions, presumably equally concerned in mental activity, may suffer injury without demonstrable effect on the individual's use of language.

Impairment of the language function due to brain lesions is known generically as *aphasia;* it takes two main forms. In one the patient can hear or read words but has difficulty in attaching meanings to them. He is *word deaf* or *word blind* without being actually either deaf or blind. In this type of aphasia the machinery for incorporating non-relevant auditory or visual stimuli into particular concepts is defective. The second type of aphasia is associated with the motor expression of language in speech or writing. The patient has no paralysis of vocal apparatus or hands, nor is his *understanding* of language necessarily affected. When he attempts to express ideas, however, he has difficulty in recalling the appropriate terms in which to clothe them.

Word deafness and word blindness are designated *sensory aphasia.* They appear, according to the findings of some investigators, to be distinct from one another anatomically as well as functionally. Word deafness is attributed by these investigators to lesions in the temporal lobe (superior or middle gyri), while word blindness (also known as *alexia*) is attributed to lesions in the parietal lobe (inferior gyrus). The affected regions in the association areas are contiguous to the sensory areas concerned in hearing and seeing respectively, and the inference is that the impulses by which sense impressions due to words are distributed from the sensory areas to their appropriate stations in the association areas have to pass through these particular regions on their way. It is highly interesting that the lesions are usually unilateral, being confined ordinarily to the left cortex (in right-handed persons). Since the sensory areas are bilateral, this fact implies a curious passing over of half of all language-bearing afferent impulses to areas of concentration in one half of the cortex. (Some investigators have argued that the associative processes in general are similarly concentrated in the left cortex in right-handed persons and in the right cortex in left-handed.)

Motor aphasia also takes two forms—difficulty in organizing speech (*aphemia*) and difficulty in organizing written language (*agraphia*). Speech impairment is the commonest of all *aphasias.* It frequently results from rupture of the middle cerebral artery. The frontal lobe is usually the site of lesions resulting in motor aphasia, a fact first recognized more than a hundred years ago (Bouillaud, 1825). Broca later went so far as to designate a restricted region in the third frontal gyrus on the left side as the "speech center," a fact which led to the practice of calling that gyrus "Broca's convolution." The *agraphia* center has been located by various investigators in the first or second frontal gyri, in close juxtaposition to the motor area.

All the knowledge we have regarding the localization of the various language functions in the cortex is the result of correlation of language defects studied during the lifetime of patients with the location of lesions observed postmortem. Accumulation of information by this method is slow and tedious, and it is perhaps to be expected that the earlier conclusions should be called in question to some extent by later findings. As a matter of fact, the present trend of opinion is to the effect that the various language areas are less sharply circumscribed than was formerly thought to be the case. Larger areas and less exact boundaries are now postulated, although location of the areas in the left hemisphere (in right-handed persons), and of the different areas in the lobes to which first assigned, has been confirmed on the whole.

CORTICAL CONTROL OF INHERENT REFLEXES.

An important feature of cortical function is the control this region possesses over the automatic reflex operation of the lower parts of the central nervous system (page 124). We know from experience that we can inhibit many reflexes volitionally. For example, one can suppress the reflex of coughing or sneezing so long as the irritation is not too strong. Many other reflexes can be inhibited similarly, although it is noteworthy that the inhibiting influence must be brought to bear prior to the initiation of the reflex or the latter will run its course before the impulses from the brain by which the inhibition is established can arrive at the point in the reflex path where they play their part.

The mechanism of this type of inhibition is thought to be precisely the same as that already pictured in connection with automatic inhibition in certain spinal cord reflexes (page 694). In this situation, as in that, to a stream of impulses passing or about to pass over a reflex path, an additional stream is added from another source. The source of the additional stream in this case is the cortex. The two sets of impulses in combination are assumed to be so timed that each individual disturbance falls in the relative refractory period of its predecessor, and is thereby so reduced in size as not to be able to traverse some synapses in the path. Since no impulses can pass there is complete suppression of reflex activity. It should be noted that some reflexes, particularly coughing and sneezing will "break through" the inhibition if the irritation becomes too strong. In other words, one will sneeze or cough in spite of efforts to refrain from doing so. The inference is that the strong irritation brings into play so many nerve paths that the volitional effort cannot extend effectively to all of them; some consequently remained unblocked, establishing the reflex.

Control of Cortical Centers by Cortical Centers.—Allied to the above phenomenon is a restraining influence exerted by some established

concepts over others. One of our familiar mental functions is the repression of behavior to which selfish considerations incline us by the coming to the fore of other considerations of a less personal nature. That this repression is a typical inhibitory phenomenon is indicated by the results of intoxication, alcoholic or otherwise. The consensus of opinion is that intoxicants depress cerebral function progressively, beginning with the least personal concepts, and extending in order to those that are more personal, hence more selfish. Thus, an early effect of intoxication is the release of selfish tendencies by the depression of cortical functions that would otherwise restrain them.

AWARENESS AND VOLITION.

Awareness or *consciousness* are names given to the faculty by virtue of which we know something of what is going on within our cerebral hemispheres in connection with the flow of nervous impulses over cortical paths. *Volition* is the faculty by which we determine to some degree the course to be taken by impulse streams both within the cortex and from the cortex to the periphery. Although these are presumably physiological functions, they are at the present time outside the scope of physiology, in that no characteristics of nervous functioning known to us give any workable suggestion as to how they are carried on.

Summary.

Under the term *mind* are grouped all processes occurring in the cerebrum. The "conscious mind" includes all such as can be explored by introspection; the "subconscious mind" such as cannot be thus explored. Mind is defined biologically as the central mechanism of selective reactivity.

Memory is defined as retention within the cerebral cortex of a state due to cortical nervous activity, in readiness for later release in the form of discharge of efferent impulses. It is significant as providing the background of experience on which successful choice is based.

The mind is so constituted as to deal not with sense impressions as such, but with interpretations based on them, known as *percepts*. When the latter are not in accord with fact they give rise to *sensory illusions*.

Associative memory is the cortical property by which relevant percepts are organized into group-percepts, designated *concepts*.

Decortication (successful in animals as high as dogs) abolishes all reactions in which the element of choice enters, together (presumably) with all nerve functions included under the designation *conscious mind*. Strictly automatic reflexes are in the main unimpaired.

Acquired reactions resemble automatic reflexes in being prompt and purposeful responses to immediate receptor stimulation. They are commonly evoked by "anticipatory" stimuli, and are understood to be mediated through the agency of *concepts*, built up ordinarily by selecting out of a mass of random experiences, repeated over and over, the particular ones that contribute toward the purposeful response. The machinery of selection is assumed to be associative memory. The process of reaction building is *learning*.

Man, and to a limited extent other organisms as well, is more or less able by the exercise of the faculty of *reason* to organize correct reactions to novel situations on the basis of previous experience as a whole. The occasion for resort to "trial and error" is thus lessened.

The flow of nervous impulses in an acquired reaction is pictured as proceeding from the receptors whose stimulation evokes the reaction to the corresponding sensory area of the cortex; thence to the association area in which the concept underlying the reaction resides; from this association area the flow proceeds to the appropriate portion of the motor cortex; thence by efferent discharge to the effectors concerned in the reaction.

The consummation of an acquired reaction does not impair the ability of the underlying concept to function subsequently; on the contrary, repetition of acquired reactions tends to facilitate their performance.

Strictly automatic reflexes, inherent in the nervous structure of the organism, and hence not dependent for their existence on the circumstances in which it happens to be placed, are known as *unconditioned reflexes* (Pavlov).

Conditioned reflexes are similar to the above in motor expression, but are evoked by other stimuli than those normally effective. A conditioned reflex tends to be established whenever the organism is subjected repeatedly to some specific "neutral" stimulus at or just prior to the time an inherent reflex is being normally evoked in it. Conditioned reflexes are thus dependent on definite environmental situations.

The salient factor in establishing conditioned reflexes is the *temporal relationship* between neutral and inherently effective stimuli. When two sets of impulses from such sources impinge on the cortex concurrently, and the concurrence is repeated several times, they become associated into something functioning like a concept; this takes place in spite of the fact that the two impulse streams are intrinsically quite irrelevant.

Primary conditioned reflexes are established only in connection with inherent reflexes; *secondary conditioned reflexes* may be established, however, by relation with primary.

Conditioned reflexes decline and ultimately disappear unless *rein-*

forced at intervals by repetition of the combination of stimuli to which they owe their origin.

Conditioned reflexes may be *extinguished* by prolonged repetition at short intervals of the conditioned stimulus, without any interpolation of the inherently effective stimulus.

Automatisms, or *habits*, are acquired reactions which, by repetition, have come to resemble inherent reflexes in the promptitude and certainty with which they are performed following receipt of the appropriate stimuli; also in the non-participation of volition as a guiding factor.

Language consists of arbitrarily selected auditory and visual symbols associated by mutual consent with the various sense impressions, percepts, concepts and remembered motor expressions which make up the content of mind. The functions of language are to facilitate direct communication among individuals and to extend individual experience beyond the range otherwise possible. The process of language learning corresponds in main features with the establishment of conditioned reflexes.

The faculty of associating percepts and concepts with words is of great significance in making elaborate mental activities possible.

Aphasia is an impairment of language function due to brain lesion. It may take the form of word deafness or word blindness (sensory aphasia) or may be a defect in language expression by speech or writing (motor aphasia). There is evidence indicating each type of aphasia to be associated with lesions in particular cortical areas.

The cortex may inhibit inherent reflexes provided it begins to discharge its stream of impulses before the reflex is actually in operation. The inhibition is presumed to be due to the simultaneous impingement of two impulse streams upon one nerve path, with the result that individual impulses are reduced in size by falling in the relative refractory phases of their predecessors.

An allied phenomenon is the repression of reactions due to concepts of a personal character by inhibitory influences from cortical areas in which reside concepts less personal in nature. The display of selfish tendencies in early stages of intoxication is commonly attributed to a depression of the less personal restraining influences by the intoxicants.

Awareness and *volition* are cortical faculties which physiology is unable at present to correlate with any known characteristics of nervous functioning.

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CHAPTER XL.

CEREBRAL FUNCTION: AFFECTIVE STATES; NERVOUS FATIGUE; SLEEP.

AFFECTIVE STATES.

The mental life includes various *affective states* (known also as feelings or emotions) which play perhaps as important roles in determining the relation of the individual to his environment as the purely intellectual faculties discussed in the last chapter. Too little is known of the inherent nature of emotions or of the cortical processes underlying them to enable physiology to take much account of them. Yet certain features are of such definite physiological interest as to merit at least brief discussion.

Among other qualities displayed by affective states is that of serving as an *urge to action*. One of the striking facts about behavior is that any organism reacts more energetically to a given situation when moved thereto by emotion than when subject only to intellectual impulsion. A feature of cortical reactions already described is that the impulse streams by which they are mediated are *augmented* during their passage through the association areas of the cortex (page 722). The presence of affective states appears to contribute somehow to making this augmentation particularly effective. Thus, one who studies human behavior cannot fail to be impressed with the extent to which vigorous reactions, particularly when in response to inherently trivial stimuli, depend on the awakening of affective states of one sort or another. So slight a stimulus as a glimpse of a distant clock face may, for example, set one running vigorously to catch a train, provided a sufficient incentive in the form of an affective state is operative.

Intense emotions tend to find expression in marked restlessness; an agitated person paces the floor, perhaps wrings his hands, and often gives voice to strong but irrelevant language. Such aimless activities are largely automatic, but are not conspicuously serviceable. In fact, about the only biological significance that can be attributed to them is that when the organism is confronted by a situation to be solved only by the method of "trial and error" the more restless it is the better is its chance of blundering on the correct reaction (page 721).

Receptor Stimulation and Affective Tone.—Certain classes of receptor stimulation are characterized inherently by more or less marked

affective tone, as already pointed out (page 493). Sensations of pain, hunger, thirst, warmth and cold, and in human beings smell, for example, invariably arouse affective states. Sight and hearing, in contrast, have little or no inherent affective tone, although particular sights and sounds may acquire it by associations causing them to become merged into percepts or concepts which carry it. To illustrate: Nothing in the sight of an opaque red liquid is inherently evocative of horror or disgust, yet many persons experience these emotions whenever they encounter such a liquid under conditions leading them to think it may be blood. The explanation is invariable a history of pain, discomfort or gruesomeness associated with blood, either as experienced personally or as learned of from another. The thought of blood has thus become merged into concepts which include in their make-up elements carrying strong affective tone; every contact with blood brings into the foreground of consciousness an entire concept, with its burden of affective tone.

Affective States in Relation to the Autonomic System.—A fact of great biological importance is that affective states are attended by activity of the autonomic system. This appears to be invariably true. The autonomic system is concerned, as already pointed out (page 131), with processes on which bodily well-being depends. Affective states likewise owe much of their significance to their relation to bodily well-being. Pleasurable emotions, as a class, are displayed in connection with the satisfaction of individual or racial needs. Painful emotions, on the other hand, come into play in situations in which danger threatens either the individual or the species. Through the arousing of the autonomic system in time of emotion the bodily processes are rallied in a manner suited to cope with the situation to which the emotion owes its origin.

With each type of emotion a particular set of autonomic nerve paths goes into action. The least-marked of the relationships between emotions and autonomic discharges is in the case of pleasurable emotions associated with individual well-being. In the main the autonomic discharges attending these appear to pass over *cranial parasympathetic* paths. One who is full-fed and at ease usually shows good digestive power and well-flushed skin (page 131). Pleasurable emotions associated with racial well-being are also attended by parasympathetic discharges. The particularly cogent emotions of this group, those that form the basis of sexual excitement (page 750), are related to discharges over *sacral parasympathetic* paths.

Painful emotions (rage, fear, anxiety and specific emotions attending nociceptive stimulation) go hand in hand with particularly striking autonomic discharges, all of which are over *sympathetic* pathways. Cannon has called particular attention to the effectiveness of discharges over these pathways in rallying the energies of the

body to meet emergencies. At such times the neuromuscular system is called on particularly. The subjoined table of effects of generalized sympathetic discharge shows clearly how these tissues tend to be favored, even at the expense of the visceral organs. The cessation of digestive activity is obviously significant only as a reaction for avoiding unessential energy expenditure; the high arterial pressure, augmented heart, relaxed bronchioles and sugar-mobilizing liver are clearly reactions favoring neuromuscular effectiveness. The table presents, at the same time, a striking picture of a frightened or angry organism, thus emphasizing the relation of emotions to activity of the autonomic system.

EFFECTS OF GENERALIZED SYMPATHETIC DISCHARGE

Hair	Erected	Pilomotor excitation.
Skin	Pale	Cutaneous vaso-constriction.
Pupils	Dilated	Excitation of dilator pupillæ.
Salivary glands	Inactive	Direct inhibition; vaso-constriction.
Bronchioles	Relaxed	Direct inhibition.
Heart	Augmented	Direct excitatory action.
Arterial pressure	High	Vaso-constriction.
Alimentary tract	Inactive	Direct inhibition; vaso-constriction.
Adrenals	Discharging	Direct excitation.
Bladder	In strong tonus	Direct excitation.
Sweat secretion	Copious	Direct excitation.
Glycemia	Present	Mobilization of sugar by liver.

NERVOUS FATIGUE.

Synapses are very susceptible to fatigue, as has already been pointed out (page 114). The primary effect of this, so far as it can be pictured, is to make the resistance of synaptic junctions higher than before, either blocking completely the nerve paths of which they are a part or requiring a different and more effective timing of the individual impulses making up the impulse stream (page 125), so that the synapses may continue to be traversed in spite of their heightened resistance. That *nerve fibers* are indefatigable has been stressed previously (page 108). The third group of elements in nerve paths, the *cell bodies*, are presumed to have no active role in impulse conduction (page 116). It would appear to follow, therefore, that all phenomena of nervous fatigue should be explicable in terms of heightened synaptic resistance.

Two main *subjective symptoms* of fatigue are recognized: The first is the occurrence of *sensations of weariness;* the second is the presence of a *sense of effort* in mental and physical activity. Sensations of weariness take a definite place in consciousness, and by analogy with other sensations would be inferred to be due to streams of afferent impulses originating in specialized receptive structures; perhaps set up by accumulation of lactates within them. It is conceivable that muscle-sense receptors, or receptors similar in location

but distinct in function, serve to mediate sensations of weariness. Positive evidence either for or against this conception is wanting. The other main subjective symptom, a sense of effort, is equally as obscure so far as its causation is concerned. One can conceive a relation between the sense of effort and heightened synaptic resistance, however, inasmuch as the effect of the latter is presumably either to block paths over which nerve impulses have been streaming, necessitating resort to previously unused paths, or to increase the resistance to a point short of complete blocking, but involving a change in the timing of successive impulses. A sense of effort can easily be imagined to accompany either of these departures from the ordinary progress of events in the nervous system.

The *chief objective signs* of nervous fatigue are a decrease in *amount* of performance and a falling off in *quality* of performance. The first finds expression in the tendency of the worker in any field to do less per unit of time as fatigue develops; the second is signalized by an increased tendency for the attention to wander; the fatigued worker is more likely to make mistakes than the fresh; if engaged in hazardous work he is also more liable to accident. Both these objective signs of fatigue can be conceived to result from heightened synaptic resistance, since both may be presumed to be due to the blocking of commonly and efficiently used nerve paths, with a consequent shift of nervous activity to less well-defined and hence less well-organized paths.

It is scarcely necessary to remind the reader that much nervous activity is *inhibitory*. Fatigue of inhibitory paths tends to release or accentuate reactions ordinarily held in abeyance. Thus a fatigued person is likely to display irascibility under circumstances in which he would hold himself in check if not fatigued.

Recovery from Fatigue.—If the theory of fatigue is correct which attributes it to accumulation of metabolites in or about sensitive structures, the obvious basis for restoration is a discontinuance of activity to permit the recovery stages in metabolism to overtake those to which the fatigue is due. The structures presumed to be involved in nervous fatigue, *i. e.*, the synapses, are so minute, and in general so abundantly supplied with blood, that rapid restoration would be expected to follow cessation of the flow of impulse stream across them. The rate at which this will occur depends, however, on the metabolite content of the blood; since the synapses necessarily tend to come into equilibrium with the blood about them, hence may be supposed to recover rapidly to a stage determined by the concentration of the blood in metabolites, and thereafter only at the rate at which the body at large clears itself of the same.

Our common experience bears out this conception in so far as we observe mental activity to be depressed by great physical fatigue, whereas purely mental fatigue due to prolonged intellectual activity

without accompanying physical exertion, is often relieved promptly and markedly by a brief period of diversion.

Various phenomena, commonly attributed to nervous fatigue, are not satisfactorily accounted for in the above terms. The gradual lowering of nervous efficiency, resulting from long periods of application to absorbing duties, for which the remedy is usually a fairly long vacation, suggests a more deep-seated impairment of the synapses than simple accumulation of metabolites is presumed to bring about. Various hormones are known to play significant roles in nerve-cell environment; there is good reason to believe that the primary cause of "nerve fag" of this type may be a disturbance in endocrine gland function by which the environment of nerve cells is affected for the worse, and the recovery process a manner of life that causes the endocrine glands to resume normal functioning. Chronic gastro-intestinal disturbance, eye-strain and low-grade infections are probably frequent contributary factors also.

SLEEP.

The account of cortical function given above applies to organisms in the waking state, when the central nervous mechanism is highly sensitive to afferent stimulation, and the organism is in continuous readiness to meet environmental changes with appropriate bodily reactions. The contrary state, *sleep*, is characterized by diminished sensitivity to receptor stimulation and by a nearly complete suspension of reactivity (Piéron). Responses in which the cortex is concerned are notably in abeyance. Thus, neither conditioned reflexes, acquired reactions, nor the perfected reactions known as automatisms are manifested in the sleeping individual (exceptions may be noted in somnambulism, which is, however, not a typical sleep state). Skeletal muscle tonus, which, as pointed out earlier (page 693) underlies all effective muscular action, is also greatly reduced in most forms, as shown by the comparative limpness of most sleeping organisms. The peculiar cortical faculties of awareness, attention and volition are to all intents and purposes nonexistent in the sleeping organism.

It is fairly obvious that the flow of nerve impulses over cortical paths is greatly diminished during sleep; presumably to a less volume than the minimum during wakefulness. Acceptance of this as a fact does not, however, help much toward a solution of the problems presented by sleep. We have still to inquire: (*a*) What are the factors leading to such marked reduction in cortical impulse volume, and (*b*) how the reduction is related to the peculiar phenomena of sleep; whether it is itself the main causative factor, or one of a number that interact to establish the sleep state? The answer to the second of these queries waits for the attainment of

more insight into the state of the cortex during wakefulness than we have at present. Investigators of sleep have accordingly devoted themselves mainly to the first, *i. e.*, to the study of the conditions leading to sleep and to awaking from it, and of the bodily state during sleep, as indicated by such reactions as are displayed by sleeping organisms.

Causation of Sleep. – *The Peripheral Factor.*—Studies of the cause of sleep indicate clearly that two factors interact to bring it about—one peripheral, the other central. The peripheral factor is a reduction in the volume of sleep-hindering afferent impulses. The most familiar feature of preparation for sleep in all organisms in which sleep occurs is the assumption of conditions favorable to a marked reduction in stimulation of certain classes of receptors. Details differ in different kinds of organisms. In most mammalian species, for example, postures are assumed in preparation for sleep in which *proprioceptive* stimulation is nearly at the minimum. This is not invariable, however; for horses commonly sleep standing, although the maintenance of the standing posture in animals so heavy implies a considerable volume of tonus-maintaining proprioceptive impulses; certainly well above the volume in motion when the same animals lie down. Stimulation of *exteroceptors* is reduced by closing the eyes and by the assumption of a position favorable to heat loss when the environment is warm, and the reverse when cool, thus minimizing stimulation of temperature receptors (page 448).

Particularly cogent is reduction to the minimum of impulses bearing certain qualities of *affective tone.* In man this is probably one of the chief peripheral elements in sleep. A familiar observation is that excitement and interest (also to a slightly less extent pain and discomfort) are decidedly inimical to the onset of sleep. No matter how favorable other conditions may be the persistence of these affective states inhibits sleep completely. It follows that stimuli, even though inherently trivial, which arouse emotions of this type bar sleep effectively.

It is not difficult to conceive why some emotions should hinder sleep. For one thing, those that have this effect are very potent in building small afferent impulse streams into voluminous efferent; the latter evocative of restlessness (page 734). From the muscles thus excited to more or less aimless activity streams of proprioceptive impulses are set up. Furthermore, affective states are attended by discharge of impulses over the autonomic system. Visceral disturbances of one sort and another are thus brought about by which, in turn, stimulation of visceroceptors may be caused (page 480). Any afferent impulses thus aroused will add themselves to the proprioceptive impulses resulting from restlessness, with the effect that from small, perhaps inherently trivial, receptor stimulation, provided it carries the right kind of affective tone,

large volumes of afferent impulses may be caused to impinge upon the cortex.

Lessening of the volume of afferent impulses is thus seen to be an important antecedent to sleep. It is altogether likely that whenever the volume is reduced below some critical level sleep results from the operation of this factor alone. The easy sleep of infants and of well-fed cats is thus accounted for. Conversely, augmenting the volume of afferent impulses counteracts sleep very effectively. This applies particularly to proprioceptive impulses. It has been shown recently (Kleitman) that muscular activity banishes desire for sleep, even in persons who have been continuously wakeful for four days or more, and who have the greatest difficulty in keeping awake whenever bodily activity is discontinued.

The Central Factor.—Common experience teaches that the organism is more susceptible to sleep at some times than at others; furthermore, the *depth* of sleep is variable; we readily make distinction between deep and light slumber. These differences are clearly not due, at least not usually, to differences in the volume of afferent stimulation. They are consequently not referable to the peripheral factor, but must be due to changes within the organism, and imply the existence, therefore, of a central factor in sleep. The precise nature of this factor can only be inferred, although we have every reason to suppose *fatigue* to be an important element in it. The conception of synaptic fatigue and its consequences, given above (page 736) points directly to this conclusion; many of our familiar experiences support it; as, for example, the pronounced sleepiness following fatiguing muscular exercise. It is true that the desire for sleep is banished for the time being, even in a fatigued person, by muscular activity (see above) but the desire returns as soon as quiet is resumed, and with increasing intensity the longer sleep is postponed.

One can account for most of the familiar facts of sleep in terms of fatigue as the chief element in the central factor, but some phenomena appear to involve other elements. For example, the somnolence that overtakes many persons after a full mid-day meal can scarcely be attributed in all cases to fatigue. The indication is that the pronounced splanchnic vaso-dilation induced by the meal reduces arterial pressure to a level of incipient cerebral anemia (page 336). That a material falling off in blood flow to the cortical cells might tend to induce sleep is readily conceivable in view of the readiness with which fainting ensues on a more exaggerated cerebral anemia. To what extent the circulatory element enters in bringing on the ordinary sleep of night is open to question. Certain investigators (Howell) have postulated an important role; others (Shepard) consider the observed circulatory changes to be effects of sleep rather than causes.

There remains the question of whether additional unknown elements are involved in the central factor; elements called into being by the mere fact of wakefulness, regardless of the state of the body in respect to fatigue, or of the character of the cerebral blood flow. One such element has been postulated (Piéron) under the designation *hypnotoxin*. This is supposed to be a distinctive sleep-inducing metabolite of nervous tissues, produced during intensive activity of nervous centers, and given off gradually into the cerebrospinal fluid. In support of this postulate is the finding that cerebrospinal fluid taken from dogs after prolonged wakefulness produces somnolence in normal dogs when injected into the fourth ventricles of the latter. "Hypnotoxin" is not thought of as particularly significant except in prolonged wakefulness. The normal process of falling asleep night after night cannot be explained in terms of it.

Perhaps as satisfactory a conception as can be held in the present state of knowledge is that the normal flow of nervous impulses, inevitable to the awake cortex, induces synaptic fatigue, which becomes more marked as wakefulness continues; the central factor tending to sleep thus becomes progressively more potent. Fatiguing activities, either of mind or body, must be presumed to accentuate the effect. But the more pronounced the central factor the less does the volume of sleep-hindering afferent impulses have to be reduced in order for sleep to set in. Hence an adjustment of the peripheral factor (by the usual preparation for slumber) that would not send the newly awakened and rested organism to sleep suffices to do so at the end of the day.

To explain the fact that much cortical activity persists during sleep, especially during light sleep, the suggestion is offered (Kleitman) that only the synapses of the "highest" cortical centers are susceptible to such degrees of fatigue as are developed in the course of an ordinary day; hence these centers are the only ones to go out of function in normal sleep. Dreaming is accounted for similarly; certain cortical centers, probably closely localized, being presumed to reënter function, without involving enough centers to induce waking. The fact that many dreams occur during transition from sleep to waking agrees with this idea.

Bodily State During Sleep.—A significant feature of sleep is the reduction in skeletal muscle tonus that attends it. This is so pronounced in man that basal metabolism determinations are rendered invalid if the subject falls asleep during them (page 456). The decline in tonus is probably to be accounted for by the lessening in volume of proprioceptive impulses. The central changes attending sleep, which might be supposed to contribute by interfering with the flow of impulses over the reflex arcs by which tonus is maintained, appear not effective in this respect, as indicated by an observation cited directly below.

A fact of some importance is that skeletal muscle reflexes persist quite decidedly during sleep. These take the form mainly of readjustments of bodily position, such as movements of extremities or turning over in bed. Their occurrence indicates that the continuous maintenance of any one reclining posture, no matter how comfortable, gives rise sooner or later to afferent impulses of sufficient volume to induce reflex activity. The frequency of bodily movement during sleep has been investigated recently (Johnson and Weigand) with the finding that in a group of normal subjects the average length of "rest period," *i. e.*, the average interval during which no motions of sufficient magnitude to show on the record were made, was about twelve minutes. In other words, sleepers readjust their posture about five times an hour on the average. It should be noted that individuals differ in the average length of rest period. In the group cited above individual averages ranging from about eight minutes to about seventeen minutes were observed. When large numbers of observations are collected it is found that "the way an individual sleeps is a very definite personal characteristic." It was observed that extreme weariness (largely nervous) is followed by increased restlessness, rather than the reverse, indicating not only as suggested above, that fatigue of "higher" cortical centers does not necessarily extend to the lower centers by which skeletal muscle reflexes involving shifts of bodily position are mediated, but, on the contrary, that central fatigue, by depressing inhibitory discharges from higher centers may lead to heightening of reflex responses. (For further evidence, see Kleitman.)

So far as sleep implies an increase in synaptic resistance, the evidence indicates quite decidedly that only the synapses in the paths over which purely cortical functions are mediated are ordinarily involved.

WAKING.

The transition from sleep to waking is probably always due immediately to receptor stimulation. That is to say, the resumption of flow of impulse streams over the paths inactive during sleep is induced by an augmented influx of afferent impulses into the cortex. It is obvious from familiar experience that the volume of such impulses necessary to wake a sleeper varies with the "depth" of sleep. Indeed, criteria of depth of sleep are based on this fact. An interesting point, however, is that special stimuli of one sort or other are commonly more potent than mere stimulation volume. For example, a mother may sleep through a violent thunder storm and yet wake at the slightest cry of her child. As sleep continues the central factor becomes less effective (presumably as fatigue declines); consequently, the sleeper is more easily awakened.

After eight hours or so the central factor has receded so materially that slight augmentation of the afferent impulse stream suffices to wake the sleeper. It is probable that in course of time the cortex would become so susceptible that if no other receptor stimulation were to occur it would be aroused to wakefulness by the afferent impulses which evoke bodily position changes, as described above.

Summary.

Affective states (emotions) are biologically important in that they constitute an urge to action. In terms of cortical function, this is interpreted to mean that they facilitate the building up of voluminous efferent discharges in response to slight afferent stimulation.

Stimulation of such receptors as those of pain, hunger, thirst, and in human beings smell, is attended inherently by *affective tone*. Other stimuli, as of sight and hearing, may acquire affective tone by association with situations in which it is inherent.

Affective states appear to be attended invariably by *discharges of the autonomic system*. Pleasurable emotions associated with individual well-being are accompanied by cranial parasympathetic discharges; those associated with racial well-being are also accompanied by parasympathetic discharges; in the subgroup constituting sexual excitement, sacral parasympathetics are specially involved. Painful emotions are attended by discharges over the sympathetic system; these are of biological importance as factors in rallying the energies of the body to cope with *emergencies*.

The only known basis for *nervous fatigue* is heightened synaptic resistance. This is conceived to be due to accumulation of metabolites about the synapses. A common *subjective symptom* of fatigue, *i. e.*, a sensation of weariness, cannot be accounted for at present in terms of heightened synaptic resistance. A second symptom, *i. e.*, a sense of effort, may be pictured as attending increased synaptic resistance, because of the change in central functioning the increased resistance makes necessary. Its nature is, however, obscure.

The main *objective signs* of fatigue, decrease in amount of performance, and falling off in quality of performance, are attributable to heightened synaptic resistance, since both would be expected to follow a shift of nervous activity from commonly and efficiently used nerve paths to less well-organized paths.

Recovery from nervous fatigue is presumed to be attained by freeing the synapses of their accumulation of metabolites. This may be achieved in part by discontinuance of activity over fatigued nerve paths, and in part by ridding the body as a whole of its excess metabolites.

Certain manifestations attributed to nervous fatigue are probably

not due solely to heightened synaptic resistance, but in part to deep-seated disturbances of nerve-cell environment, as by partial failure of endocrine gland function, or other functional disorders.

Sleep is characterized by diminished sensitivity to receptor stimulation and by a nearly complete suspension of reactivity. Skeletal muscle tonus is ordinarily much reduced, and the peculiar cortical faculties of awareness, attention and volition, are essentially non-functional. A reduction in the flow of cortical impulses below the minimum volume of wakefulness is assumed to be a salient feature of sleep.

The *causation* of sleep involves the interaction of peripheral and central factors. The peripheral factor is a reduction in the volume of sleep-hindering afferent impulses. Reduction in proprioceptive stimulation and in stimulation carrying affective tone is particularly important. The central factor is less definitely understood. Synaptic fatigue, especially of "highest" cortical centers, appears to be a prominent element in it. Cerebral anemia probably contributes also to somnolence under some conditions. There is some evidence for the formation of a special sleep-inducing metabolite, *hypnotoxin*, in prolonged wakefulness.

Although skeletal muscle *tonus* is markedly reduced during sleep, skeletal muscle *reflexes* occur normally, and with some frequency, taking the form of readjustments of bodily position. Their occurrence lends support to the conception that heightened synaptic resistance as a factor in sleep does not extend beyond the cerebral cortex.

Waking is probably always due immediately to receptor stimulation. The critical afferent impulse volume varies with the depth of sleep, in other words, with the potency of the central factor. As the latter declines with the decrease in central fatigue the afferent threshold volume also falls.

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CHAPTER XLI.

REPRODUCTION.

THE GERMINAL TISSUES.

In all organisms except the lowest certain tissues are set aside early in embryonic development as progenitors of the cells from which individuals of the succeeding generation are to be derived. In the higher organisms these are localized in definite structures, ovaries in the female, testes in the male. Here they are nourished by an abundant blood supply and in periods of sexual activity grow and proliferate rapidly.

MATURATION.

The ordinary proliferation of germinal cells is similar to that of somatic cells in all essential respects; daughter cells are derived from mother cells by typical mitotic division in the sequence of cell divisions by which many germinal cells are derived from a few. In all vertebrates and most invertebrates, however, every true germ cell passes at one stage through a special *maturation mitosis* which fits it to serve as progenitor of a new individual.

The reader is referred to works on heredity or genetics for details as to the significance of maturation. All space permits to be said here is that ordinary germinal cells and somatic cells have the same definite number of *pairs of chromosomes*, a number characteristic for the species. The genesis of a new individual starts with the union of two germinal cells, male and female; if each were to contribute the full number of chromosome pairs there would be doubling in each generation, an obviously impossible situation if continued (although occasional instances are known). Doubling is avoided by the peculiar character of the maturation mitosis in which instead of each chromosome splitting into identical halves, the chromosome pairs simply separate, with the result that instead of each daughter cell having precisely the same chromosome content as its mate, and as the mother cell from which derived, each has only as many single chromosomes as the mother cell had chromosome pairs; furthermore, the mates are not alike in chromosome content (identity after maturation is possible in theory but improbable in fact). After maturation (known also as *reduction division*) typical mitosis recurs, giving four ripe cells for each germ cell to maturate.

In the male the cell undergoing maturation is known as the *sperm mother cell.* The four ripe daughter cells undergo certain modifications and become functional *spermatozoa.* In the female maturation results in a partition of the chromosomes in equal numbers, but of the cytoplasm unequally. One daughter cell retains virtually all, a negligible fraction of cytoplasm separating off with one set of chromosomes to make up the "first polar body." In the recurrent typical mitosis the cytoplasm is again retained in toto by one daughter cell, a second polar body being separated off from the ripening egg, and the first polar body dividing into two. Thus, the *egg mother cell* gives rise to one functional *ovum* and three non-functional polar bodies, each of the latter with a quota of unpaired chromosomes, but devoid of cytoplasm. The steps in maturation are indicated diagrammatically in Fig. 130.

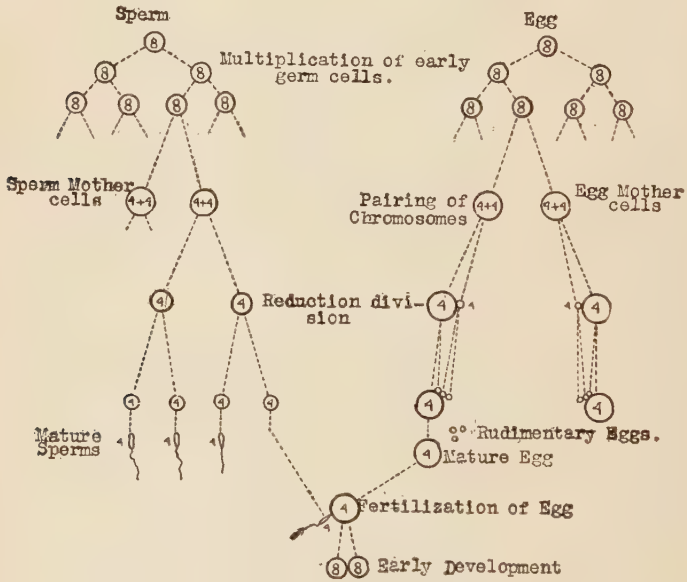

FIG. 130.—Diagram showing development of the germ cells. (Burlingame, *et al.* General Biology, Henry Holt & Co., Publishers.)

FERTILIZATION.

The act of fertilization consists essentially of the entry of a single sperm into a ripe ovum. This restores the characteristic number of chromosome pairs. The pairs are typically compatible, since egg and sperm are derived from organisms of the same (or a closely related) species. The fact that the members of each pair differ in ancestry is of the greatest significance in heredity. (For discussion, see works on that subject.)

FACTORS IN DEVELOPMENT.

The entry of the sperm also upsets the previously prevailing physico-chemical equilibrium in the ovum, initiating a sequence of processes of cell division, cell growth and cell differentiation, culminating normally in a new individual of the species. In many lower forms the power to pass from ripe ovum to functional adult by an orderly process of development is inherent in the chromosome-cytoplasm system which makes up the ovum. In any form in which this is the case the only external factors essential to the process are an effective stimulus for inducing the first cell division and the continuous maintenance thereafter of a suitable environment. Development in this manner, without fertilization, is known as *parthenogenesis.*

While the effective stimulus, except in naturally parthenogenetic forms, is normally furnished by the entry of a sperm, such simple treatment as exposure of the ovum to an environment slightly different in proportion of inorganic salts, or of a changed hydrogen-ion concentration, suffices in the lower forms in which the phenomenon has been observed (J. Loeb). The way in which the sperm operates to produce an apparently precisely similar response has not been determined as yet.

Parthenogenesis, either natural or artificial, has not been observed in mammals; it is accordingly not possible to state whether the sperm contributes to the developmental process in these higher forms any factors additional to a quota of chromosomes and a stimulus to the first cell division.

The question is of great theoretical interest. For the present purpose, however, the significant point to be stressed is that the ovum upon fertilization enters at once into a condition of unstable equilibrium leading to a succession of automatic and very complex processes of cell division, cell growth and cell differentiation, which are bound to proceed in orderly fashion to culmination in a new individual, provided suitable cell environment is maintained continuously (the introduction of lethal factors through the bringing together of incompatible chromosome pairs may sometimes defeat this). From the standpoint of physiology, the study of reproduction concerns itself, therefore, with *the conditions under which mature ova and ripe sperm are produced, the method by which these are brought together to secure fertilization and the subsequent provision of an environment for the developing organism suitable at every stage for the particular requirements of that stage.*

THE ATTAINMENT OF SEXUAL MATURITY.

The germinal tissues in human beings are set aside from the somatic very early in embryonic history. During the embryonic

and most of the juvenile period, however (page 63), they remain relatively quiescent, showing a certain amount of cell proliferation by which the total number of germinal cells increases, more or less in proportion to the growth of somatic cells, but producing no functional ova or spermatozoa prior to the onset of *puberty*. The latter period, occurring normally between the eleventh and sixteenth years, is marked by rapid development of the reproductive tissues, including both the *germinal tissues proper* and the *accessory organs of reproduction;* by the production of functionally mature ova or spermatozoa; by relatively more rapid growth of the whole

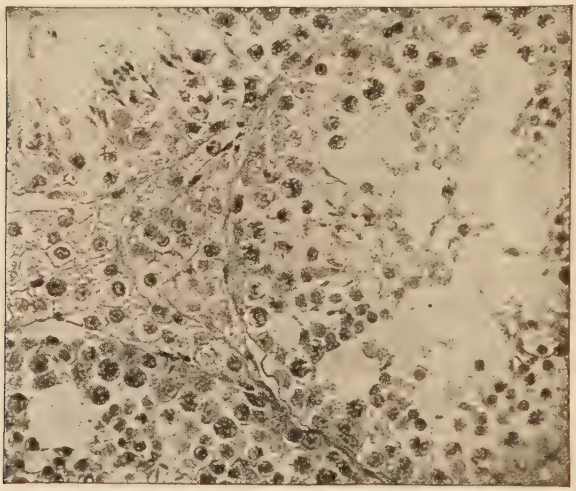

Fig. 131.—Interstitial cells of cat. Parts of three seminiferous tubules are included in the photographs. (From Schäfer's Endocrine Organs, by permission of the author.)

body than just before or at any time subsequently; by appearance of the *secondary sexual characters*, including the growth of hair on the pubes and in the axillæ, and in males on the face; enlargement of the larynx and lengthening of the vocal cords in males, so that the "voice changes;" enlargement of the pelvis and increased deposition of subcutaneous fat in females.

Factors Governing the Onset of Puberty.—There is no doubt that the various phenomena occurring at puberty are evoked by hormone action. Furthermore, the source of the hormone or hormones immediately concerned can be conclusively localized in the gonads themselves. The fact that the normal phenomena of puberty fail to develop following castration or ovariectomy is sufficient proof.

In males the interstitial cells, epithelium-like cells arranged in strands, and interspersed with the intertubular connective tissue of the testicle (Fig. 131), appear without doubt to be the secretory

cells for the hormone, accordingly constituting the "puberty gland." In females the evidence is less clear; not all forms show well-differentiated interstitial cells in the ovaries. However, the follicular epithelium (see below) has been shown to have endocrine function, and in all probability either shares with or replaces the interstitial cells in elaborating the pubertal hormone in the female.

Prior to puberty these cells are all relatively undeveloped and presumably completely inactive. The first step toward the attainment of sexual maturity consists of rapid proliferation and enlargement of the cells of the puberty gland itself. Evidently we have still to inquire what stimulus is the inciting cause of this rapid development at this particular time. The problem is unsolved as yet; some evidence indicates that hormones either from the pituitary or the pineal body may be concerned. Thus, pituitary disorders indicative of hypofunction are often attended by sexual infantilism (Froelich's syndrome) and pineal tumors have been present in cases of pronounced sexual precocity in male children. The hastening of maturity in rats by daily implants of fresh anterior pituitary substance is described elsewhere (page 207).

Under normal conditions the interstitial and follicular cells become functional some time after the tenth year and before the seventeenth. Under the influence of the hormones thus produced the series of changes described above as making up the events of puberty take place and the organism becomes sexually mature.

SPERMATOZOA.

The reproductive function of males centers around the production of spermatozoa and the introduction of the same into the reproductive tract of the female, where fertilization of one or more mature ova may occur. The sperm mother cells are formed by proliferation of germinal cells in the lining membrane of the *seminiferous tubules*. The process (including maturation) by which four functional sperm are produced by each sperm mother cell is outlined above (page 746). Individual spermatozoa are actively motile in most forms, and are also endowed with marked vitality, surviving days or, in extreme cases (bats), months under favorable conditions.

Spermatozoa are formed practically continuously after puberty in man and in most domestic animals. In many wild species sexual activity is seasonal, and in these sperm formation is in abeyance except during the "rutting" season. When active spermatogenesis is in progress it occurs at a rapid rate; the domestic cock frequently impregnates twenty or more hens daily, discharging at each ejaculation hundreds of thousands or possibly millions of spermatozoa. A single ejaculation in some mammals is estimated to contain more than, 50,000,000 sperm per milliliter. Of all the millions thus

introduced into the female reproductive tract, only 1 to 12, according to the size of the litter, fertilize ova (in some forms several spermatozoa may penetrate each ovum, but only one actually fertilizes it).

As fast as spermatozoa are formed in the seminiferous tubules they pass through a succession of relatively long tubes (the vasa efferentia, epididymis and vas deferens) to the *seminal vesicles*, accumulating either in the latter receptacles or in the tubes themselves. Secretions from the accessory reproductive glands (Cowper's gland, the prostate, and the seminal vesicles) are added, the whole making up the seminal fluid. The secretions play a necessary, but as yet undetermined, part in the insemination process.

INSEMINATION.

The process of insemination involves erection (particularly of the penis), intromission and ejaculation, the two latter constituting the male act in coitus. Erection is a vascular phenomenon, involving active vaso-dilation, supplemented in the penis by compression of the efferent vein by contraction of the ischio- and bulbocavernosus muscles (probably aided by contractions of other muscles as well), with the result that the erectile tissue becomes rigid and distended. Erection is ordinarily induced reflexly, the afferent impulses originating in receptors stimulated by distention of the seminal vesicles and adjacent tubes. Mechanical stimulation of the genitalia is also effective. The afferent paths to the cord are mainly in the pudic nerves; the efferent belong to the sacral subdivision of the parasympathetic system (page 130); in dogs and some other mammals they are in the *nervi erigentes;* in man, in fibers of the various plexuses of the pelvic region. A center in the lumbar cord is postulated as the region where the streams of afferent impulses are translated into suitably coördinated efferent streams.

The same afferent impulses as stimulate the "coitus center" in the lumbar cord also penetrate to the brain, arousing erotic sensations. Various other sensory stimuli, particularly of smell and sight, may have the same effect, setting up the affective states characteristic of sexual excitement (page 735). These rank with those set up by hunger and thirst in the potency with which they incite the organism to action. In view of the fact that no organism below the rank of man can conceivably appreciate the significance of sexual congress as a factor in racial perpetuation, the fundamental biological importance of sexual excitement is clear. Sexual excitement is attended by a play of impulses from the brain upon the "coitus center" reinforcing the effect of the stimuli direct from the periphery.

Intromission is essentially volitional in inception, although par-

tially or wholly reflex in its continuation. Ejaculation is definitely reflex, depending for its accomplishment on additional afferent stimulation of the "coitus center" from the genitalia. Impulses descending from the brain ordinarily take part in excitation of the "coitus center," but they are not necessary, since erection, characteristic "coitus movements" and ejaculation may all occur after complete section of the cord above the lumbar region.

The spermatozoa introduced into the female genital tract in coitus propel themselves by lashing movements of their "tails" into and through the uterus and along the Fallopian tubes. It has been suggested that the direction taken is determined by the ciliary movement in the tubes, the spermatozoa tending to "swim against the stream."

OVOGENESIS.

The *germinal epithelium* in the female mammal is in the outer surface of the ovary. Directly beneath this is the *tunica albuginea*, a connective-tissue layer separating the germinal epithelium from the immediately underlying *germinal cortex*. The main mass of the ovary consists of a highly vascular connective-tissue *stroma* in the spaces of which occur *Graafian follicles* and (in some forms) masses of interstitial cells (Fig. 132).

FIG. 132.—Section of cat's ovary (Schron). 1, the tunica albuginea, overlain by germinal epithelium; 2 and 3, central and peripheral stroma; 5, layer of young Graafian follicles; 6, 7, 8, enlarging follicles; 9, mature follicle; 10, corpus luteum. (From Schäfer's Endocrine Organs by permission of the author.)

Each Graafian follicle consists at first of a primitive ovum enclosed in a single layer of flattened epithelial cells. The whole follicle is derived by cell proliferation from the germinal epithelium; it takes up a position in the *germinal cortex*, immediately under the tunica albuginea. Subsequently the primary follicle cells proliferate to form a multiple layer. The ovarian stroma immediately surround-

ing each follicle also becomes differentiated into a two-layered *theca*, in which epithelium-like cells thought to be interstitial in character make their appearance. Follicle formation begins in an early embryonic stage, and appears according to evidence recently advanced (E. Allen) to continue until the menopause. Many, or perhaps all, of the primitive ova appear to pass through the process of maturation, but prior to puberty this is followed by degeneration and disappearance of the follicles in toto, so that, although follicles are being formed continuously, their number in the ovary does not increase. In rats the number in both ovaries at this stage is stated to be 10,000 to 11,000 (Arai). After puberty the same fate befalls most of the follicles, but a small percentage survive, and increase considerably in size. The increase is partly due to further multiplication of the epithelial cells making up the follicular walls, and partly to the formation of *follicular liquid* which is secreted by the surrounding cells into the follicles and distends them. The enlarged follicles sink from the germinal cortex into deeper portions of the ovary, where they appear to remain quiescent for a shorter or longer time. The ovum lies at one side of the follicular cavity, enclosed in a secondary mass of epithelial cells making up the *discus proligerus*.

OVULATION.

This phenomenon occurs at quite definite intervals in all higher forms. The domestic fowl ovulates daily during egg-laying periods; in mice and rats the interval is about four days; in the majority of mammals, including man, it is between two and four weeks; in fur seals and some large mammals normally only once a year. The intervals given apply to the organism as a whole; in forms with paired ovaries the *ovarian* interval may be twice as long.

The process begins by a further increase in size of one or more of the large, quiescent follicles described above; in the pig the increase is from 4 to 5 mm. up to 8 to 10 mm. The enlargement is accompanied by marked development of the "interstitial" cells of the follicular theca, and by considerable increase in quantity of follicular liquid; it brings the follicle to the surface of the ovary. Meanwhile the ovum maturates, unless it has done so previously, and the attachment of the discus proligerus to the underlying follicular surface thins away, leaving the former practically free.

In all mammals thus far studied, except the domestic cat, the domestic rabbit and the ferret, the follicle then ruptures spontaneously, extruding the ovum. In these three exceptional species rupture occurs only following coitus. In forms that have one young at a birth only one follicle enlarges and ruptures, the ovaries usually alternating in the action; forms that produce litters have several enlarging follicles divided between the two ovaries. The

extruded ova are caught on the fimbriæ of the Fallopian tube and begin to be carried along toward the uterus by the action of the cilia lining the tube. In nearly all mammals yet studied the descent to the uterus requires three days (in the dog the time is about a week). Exceptionally an ovum instead of being picked up by the fimbriæ may escape into the pelvic cavity where it is sometimes fertilized, leading to "extra-uterine" pregnancy.

Ovulation may be delayed or even prevented by administration of extract of anterior pituitary, as already pointed out (page 207). The relation of this fact to normal ovulation is not, however, clear as yet. The regular sequence of ovulations after the first one, at puberty, is accounted for without reference to pituitary function, as shown below.

Œstrus.—In nearly all forms except the primates ovulation is attended or shortly preceded by external signs of one kind or another. These persist for a period varying from a few hours in mice and rats to as much as three weeks in extreme cases in dogs. The period is known as *œstrus*, or "heat," and marks the only time at which sexual excitement occurs and in which impregnation takes place. (The absence of definite œstrus in human females goes hand in hand with the lack of marked periodicity in sexual excitement in the human species.)

The manifest signs of œstrus develop gradually and reach their climax before ovulation occurs. In the rat, in which the phenomena have been studied with particular care (Long and Evans), the interval between the effective beginning of œstrus, *i. e.*, the time when the male will first be accepted, and the discharge of ova from ruptured Graafian follicles averages about a day.

Various workers have shown the onset of œstrus to be due to stimulation set up within the ovary itself and connected with the enlarging follicles. E. Allen and co-workers have demonstrated the presence in the liquid taken from such follicles of a fat-soluble hormone which has the property of inducing œstrus when injected into the vessels of a female mammal (rat). In these experiments the rats used were either immature or were prevented by ovariectomy from developing œstrus normally. The follicular liquid is known to be elaborated either by the follicular or the thecal interstitial cells; consequently, we have in these cells typical endocrine gland action. A marked characteristic of this action is, however, its intermittence. A clue as to the factors responsible for this is furnished by the history of the Graafian follicles subsequent to ovulation.

The Corpus Luteum in Relation to Ovulation.—Following the rupture of a follicle the cells composing its epithelial wall (granulosa cells) increase markedly in size without further multiplication, filling the former cavity completely. The process requires three

to seven days in most forms. The yellowish mass thus produced is the *corpus luteum* (10, Fig. 132). This structure takes on important endocrine gland functions different from those of the antecedent Graafian follicles (the human species is apparently to some extent exceptional in this feature; next page). The chief of these new functions is described later. The one that interests us here is an influence exerted to inhibit the enlargement of the resting follicles (page 752) and thus to prevent both œstrus and ovulation. The corpora lutea persist a longer or shorter time, varying with the species and with whether or not pregnancy follows ovulation. Sooner or later, however, in either event, degenerative changes occur, and shortly thereafter one or more resting follicles begin to enlarge, initiating another ovulation. The evidence is fairly clear that in most forms the immediate hindrance both to œstrus and ovulation is the presence of actively functioning corpora lutea. The inference is that they form an inhibitory endocrine substance. This observation does not explain the first œstrus of puberty, nor the fact that heat in rabbits and cats subsides after a few days, even if no coitus occurs and hence no follicles rupture to be replaced by corpora lutea. It does, however, account for the interesting finding that in ferrets denied the male heat persists much longer than normal.

The interval between the beginning of retrogression of the corpus luteum and the next rupture of a mature follicle varies widely in different species. In human beings it is about sixteen days; in dogs possibly even longer. This is interpreted as the time required for a follicle of the species in question to pass from the resting to the mature state. In rats and mice, with their short œstrus cycles, demonstrable degenerative changes do not occur in the luteal bodies prior to succeeding periods of "heat." It may nevertheless be inferred that the inhibitory hormone ceases to be formed, as in the organisms in which degeneration is readily seen.

Relation of the Corpus Luteum to Implantation and Placentation.—A fact to be borne in mind is that in the course of nature ovulation is ordinarily followed by pregnancy; a fertilized ovum is to be provided by the maternal organism with a suitable environment in which to pass the successive developmental stages prior to birth and the beginning of a more or less independent existence. This environment is furnished by the uterus, on the wall of which the developing embryo becomes *implanted;* and after the early stages in part by the *placenta*, which comes also to play an important role. Both implantation and placentation involve certain preliminary changes in the uterine mucosa. These changes have been shown to be brought about by hormone action, the maturing Graafian follicles yielding a hormone that initiates the process, and the corpora lutea one that carries the changes on to a functionally effective stage.

Whether fertilization takes place or not the follicular hormone is produced precisely as usual, and the luteal also for a time; consequently the uterine changes preparatory to implantation and placentation run their course. The degenerative processes that occur sooner or later in the corpora lutea when pregnancy does not follow ovulation have been shown never to set in until after sufficient lapse of time for normal implantation to occur. As soon as luteal degeneration begins the uterus reverts to its resting state. The cycle of uterine changes following ovulation without pregnancy is known as "pseudo-pregnancy," or as the "progestational stage."

MENSTRUATION.

Although in the human female ovulation is not attended by objective signs of œstrus, the basic phenomena, *i. e.*, enlargement of a Graafian follicle, rupture of the same and subsequent formation of a corpus luteum, occur essentially as in other mammalian forms. Hormones similar in their effect on the uterus are also produced. Placentation in all primates differs, however, from the same process in other mammals in that in the former the uterine bloodvessels actually come to open into the intervillous spaces of the placenta. Coördinated with this difference is the fact that in primates the uterine alterations following ovulation proceed regularly to a stage verging on breakdown of the bloodvessel walls, with consequent hemorrhage. Although evidence on the point is scanty, degeneration of the corpus luteum appears to set in *after* the stage of uterine hemorrhage is reached (Corner). If normal pregnancy occurs the processes of implantation and placentation supervene to prevent more than possibly a slight hemorrhage, the latter being occasionally seen at the first menstrual period following conception. In the absence of pregnancy the hemorrhage becomes considerable; it is accompanied by more or less sloughing of uterine epithelium; the whole constituting the *menstrual flow*. The process usually begins about twelve days after ovulation in human females and requires about four days for completion. During its later stages the uterine mucosa undergoes processes of self-repair, returning thus to the resting condition. While menstruation is in progress the entire genital tract is more or less congested with blood; the nervous system usually gives indication also of hyperirritability. The cause of these vascular and nervous manifestations is obscure.

Human Corpus Luteum Secretes Follicular Hormone.—The absence of definite œstrus in human beings with its accompanying lack of marked periodicity in sexual excitement has been difficult to account for in view of the presence in the human female of typical Graafian follicles, which become filled with liquid at intervals, just as do the follicles of other forms. A clue may conceivably be had by the finding (Allen and Doisy) that fat-soluble extracts of *human corpus*

luteum stimulate the onset of œstrus in experimental rats precisely as do similar extracts of ripe follicular liquid (page 753). Corpora lutea of other mammals tested do not show the same property. If the hormone that normally stimulates the follicles to the ovulation process is produced in human females by both the follicle cells themselves and the luteal cells, as appears from this observation, the stimulus which acts in lower mammals to produce œstrus is constantly present in human females. To account for ovulation being as periodic in the human species as in those that show œstrus, it must be assumed that the human corpus luteum is like that of other mammals in producing the hormone inhibitory to ovulation (page 754) and also that this hormone is potent to prevent the ovulation hormone simultaneously present in the corpus luteum from exerting its normal influence on ovulation, although not on its action in causing or favoring sexual excitement. When degenerative changes develop in the luteal body all its hormones may be assumed to cease being formed. The ovulation hormone present in the follicles then becomes effective, initiating a new ovulation. This conception harmonizes with the familiar fact that sexual activity is often at the minimum during the menstrual period, since degeneration of the corpus luteum sets in then removing it as a source of ovulation hormone, and the change of another follicle from the resting to the active state is just getting under way

THE REPRODUCTIVE CYCLE IN THE ABSENCE OF PREGNANCY.

This may be summarized for human females as follows: Degenerative changes take place in the corpus luteum of the preceding cycle, with consequent disappearance of the ovulation-inhibiting hormone; under the stimulus of the small quantity of ovulation-inciting hormone constantly present in the resting follicles one of the latter begins to enlarge, becoming mature in about sixteen days; it then ruptures spontaneously, giving place in three to five days to a functional corpus luteum (Schroeder). Under the influence first of a hormone produced by the mature follicle, and later of a similar hormone of the corpus luteum, progestational changes occur in the uterus, adapting it for implantation of an embryo and for placentation. These changes continue for about twelve days, culminating in the menstrual hemorrhage. During this hemorrhage degeneration of the corpus luteum sets in, initiating another cycle. Meanwhile the ovum extruded from the ruptured follicle has been carried down the Fallopian tube to the uterus, requiring probably three days for the passage, and has lain in the uterus perhaps two or three days more, before degenerating and disappearing.

CONCEPTION.

The spermatozoa introduced at coitus move into the uterus and thence into and along the Fallopian tubes (page 751). If an ovum is anywhere present sperm encounter it comparatively soon (within three hours in some species, C. V. Taylor). When coitus occurs early in œstrus fertilization takes place in the distal portion of the tube (this is the normal state of affairs). The more coitus is delayed the nearer the ovum will be to the uterus when sperm make contact with it. So far as known, the rate of descent of the ovum along the tube is the same whether fertilized or not, being determined by the ciliary activity of the tubal lining. Cleavage begins promptly, an ovum fertilized in the distal tube having progressed at least as far as the morula stage by the time the uterus is reached.

In the human species coitus does not relate itself definitely to ovulation except fortuitously. The position of the ovum in the genital tract at coitus, or whether an ovum is present at all or not, is a matter of chance. Consequently, the occurrence of conception in a large percentage of fruitful inseminations depends on the survival power of the spermatozoa. Evidence exists indicating that human spermatozoa may persist in the female reproductive tract as long as three and a half weeks (Dührssen, cited by McMurrich). It appears from extensive studies made in Germany during the World War, however, that coitus is rarely fruitful between the degeneration of the ovum, about five or six days after ovulation, and the next succeeding menstruation (for references, see Corner). The indication is either that survival for as long a period as stated above is exceptional, or that the menstrual process is unfavorable to survival of spermatozoa, even though they may have moved beyond the uterus itself into the Fallopian tubes.

GESTATION.

In ovulation not followed by conception the unfertilized ovum descends to the uterus and presently degenerates, having no influence, so far as known, on the reproductive cycle. When conception occurs, on the other hand, the developing embryo exerts a very profound influence on the subsequent course of events in the reproductive tract. The first of these events are implantation of the embryo on the uterine wall, and the development of the placenta, the latter structure providing the means for interchanges of nutritive materials, of hormones and of waste metabolites between fetal and maternal blood. Prior to placentation the embryo subsists on its contained store of nutrients. This store is limited in mammals as compared with most other groups. Implantation depends on

the presence of the embryo in contact with a specially prepared uterine wall (page 754). Placentation in man is a process to which the uterus contributes a portion and the fetus a portion. The interesting fact has been established (L. Loeb) that the adequate stimulus to cause the uterus to form its portion of the placenta (*i. e.*, the decidual) is the mechanical contact of the embryo. A decidual growth can be induced during the progestational period by simply placing an indifferent foreign body in the uterus.

Some cells of the fetus produce and pour out a hormone whose effect is to prolong the functional life of the corpus luteum. Instead of degenerating at the end of the progestational stage, as after ovulation without conception, the corpus luteum continues actively functional so long as the fetus remains in the uterus. Ovulation is thus prevented during the entire gestation period.

The formation of the placenta and the development of fetal blood provide the essentials for nutrition of the fetus; it accordingly develops along the lines set by its heredity, subject to such influences as may be brought to bear through the maternal blood. An important feature of the situation is that maternal and fetal blood do not actually mingle at any time; they are always separated by the membranous surfaces of the chorionic villi. Consequently only such constituents of either blood enter the other as pass through these membranes, all the principles that govern passage of materials through membranes applying fully in this instance.

PARTURITION.

Continued development of the fetus carries it, within a time characteristic of the species (ranging from nineteen days in the mouse to twenty months in the elephant), to a stage in which the protection afforded by the maternal uterus is no longer essential. As this stage is reached retrogression of the corpora lutea (one for each fetus) sets in. The inference is that the fetal hormone, by which the luteal bodies are maintained in functional activity, falls off as normal term approaches. The conclusion seems warranted that cessation of luteal hormone formation precipitates parturition, although positive evidence to that effect is not available. The act of parturition consists primarily of strong contractions of the smooth muscle walls of the uterus, supplemented more or less by vigorous expiratory efforts with closed glottis. In the opinion of a number of investigators the immediate stimulus to uterine contraction is afforded by the postpituitary hormone (page 205), which is thought of as being secreted in exceptionally large amounts at this particular time. The disappearance of luteal hormone is conceived as setting free influences (perhaps by a change in the metabolism of some of the tissues; F. H. A. Marshall) which lead to heightened postpituitary activity.

In human females the fetus reaches "term" in approximately two hundred and sixty-four days, reckoning from the ovulation at which gestation is initiated, or two hundred and eighty days after the last menstrual period preceding conception. Parturition is likely to occur at any time thereafter, or under special conditions (premature delivery) considerably before. The uterus is a smooth muscle organ innervated through the autonomic system, and more or less susceptible, therefore, to influences, emotional and other, such as are attended by strong autonomic discharges.

Delivery is attended with severe pains, particularly distressing and prolonged in primiparæ, in whom they may endure spasmodically from ten to twelve hours to more than a day. The stretching to which the maternal tissues are subjected accounts for much of the pain; consequently subsequent deliveries are somewhat more easily borne, the tissues not regaining the pristine tightness after their first stretching. Following delivery of the fetus the uterus continues to contract until the placenta, together with the fetal membranes, the whole constituting the *after birth*, is expelled. As the placenta breaks away from the uterine wall it leaves open blood sinuses behind it. The quickly fatal hemorrhage which would otherwise ensue is controlled more or less completely by continued firm contraction of the uterus.

LACTATION.

One of the phenomena of puberty in the female is enlargement of the mammary glands: This action is attributed to the interstitial hormone (page 749). It does not proceed to the point of functional activity, for which further development of the gland tissue is requisite. The stimulus to this additional development can be stated almost without doubt to be provided by functionally active corpora lutea, and to be a hormone action; but whether due to the same hormone as suppresses ovulation or another one cannot be said. Various lines of evidence point to a luteal hormone as the stimulus to mammary gland development. One of the best demonstrations is that of Ancel and Bouin, who took advantage of the fact that in the rabbit ovulation does not occur spontaneously, but only after coitus. In their experiment they secured coitus without pregnancy by the use of a sterilized buck. The resultant ovulation was attended by typical corpus luteum formation. The lutea continued functional during a considerable period, and the mammary glands developed coincidently; almost to the point, in fact, of beginning milk secretion. A similar phenomenon is often seen in female dogs, the progestational period in this species lasting nearly as long as true gestation, and hence long enough for mammary gland development to proceed virtually to the full.

In the normal course of events the mammary glands in human females become functional nearly simultaneously with parturition. The first secretion formed by them is not true milk, however, but a liquid known as *colostrum*, which differs from true milk mainly in having a nearly negligible content of casein. Colostrum also contains many cells (presumably leukocytes) loaded with fat; these are not in evidence after the proper milk secretion gets under way. How the change in gland metabolism is brought to pass by which casein comes to be actively synthesized, and the other differences between colostrum and milk established, is not known. There is some evidence that the mechanical stimulation of suckling may be a factor. The change normally occurs about the third day after parturition, but it is stated that if a child is put to the breast prior to that event true milk secretion begins earlier. On the other hand if the child is born dead or is not suckled for any reason true milk is formed at about the normal time. The breasts become considerably congested, due to the accumulation of fluid in their lacunæ; it is conceivable that the mechanical stimulation thus afforded may be adequate to induce the change.

The mammary glands are, as stated earlier (page 149), looked on as modified sebaceous glands. The cardinal feature of the action of glands of this type is that the act of secretion consists of sloughing of portions of the cells directly into the duct, carrying the previously formed secretion with them. In such glands as the mammary, which can give out a large quantity of secretion in a short time, this type of secretion implies a storage capacity virtually as large as the potential volume of secretory product. Cell disintegration and cell repair are processes that cannot be speeded up materially. It follows that they must go on continuously between one emptying of the lactiferous ducts and the next one, refilling the ducts and alveoli in the interval. The evidence is clear that in most species, if not in all, continuance of lactation after it is once started depends solely on periodic withdrawal of the accumulated milk. To maintain secretion at the maximum, withdrawal must be complete whenever it is begun and must occur at intervals adjusted to the rate of milk formation. If any of the alveoli fail to be emptied completely the subsequent accumulation of milk distends them unduly, with the result that less milk tends to be formed subsequently. This fact explains the adjustment of the milk yield to the size of the litter, or in mothers with only one young, to the size and strength of the offspring. Complete cessation of suckling or of milking of cattle is followed by unrelieved distention until the glands cease functioning, which they do shortly, reverting to their resting state. Abrupt discontinuance of milk withdrawal is provocative of much discomfort to the mother; the practice usually prevails, therefore, of tapering off gradually.

Relation of Lactation to Pregnancy.—The retrogression of corpora lutea by which the period of gestation is terminated clears the way for resumption of ovulation (page 754); the result is that in many species ovulation attended by true œstrus follows parturition closely. This occurs in mice and rats, for instance, and in fur seals, the females of the latter species being pregnant practically continuously from puberty onward. The onset of a new pregnancy does not appear to influence lactation, except in so far as the burden of nourishing two litters simultaneously, one *in utero* and the other at the breast, may overtax the maternal organism.

In human females menstruation (indicative of ovulation) is resumed fairly early in the lactation period in about 40 per cent of individuals, and within nine months in practically all (Marshall). There appears to be a correlation with age, in that younger women tend to resume menstruation earlier than older. The explanation of this variation is not known.

THE MENOPAUSE.

This period, which marks the termination of reproductive capacity in women, comes on between the fortieth and fiftieth year, on the average at about the age of forty-five years, on the whole earlier in warm climates than in colder. Bodily manifestations associated with it may occur during a period covering three to five years. The immediate cause is atrophy of the ovaries; ovogenesis with attending formation of Graafian follicles ceases, consequently neither follicular liquid, with its contained hormones, nor active corpora lutea are produced. The interstitial tissue also disappears, and the entire organ shrinks to rudimentary dimensions.

Obviously all bodily functions dependent for their continuance on ovarian activity are discontinued. Ovulation and menstruation cease after a period of irregular appearance; degenerative changes occur in the accessory reproductive organs (Fallopian tubes, uterus, external genitalia and mammary glands). The autonomic nervous system is also in an unsettled state; consequently, cardiac and vaso-motor disturbances, gastro-intestinal irregularities, unseasonable sweating and psychic disorders of greater or less magnitude occur. The reason for this autonomic unsettlement has not been made out.

GROWTH, MATURITY, SENESCENCE AND DEATH.

The growth period, with its special metabolism, has been discussed earlier (page 61). The rate and duration of active growth vary in different species, and are subject within the species to various influences, most of which have been pointed out in preceding chapters. In man the average course of growth is as indicated in Fig. 133.

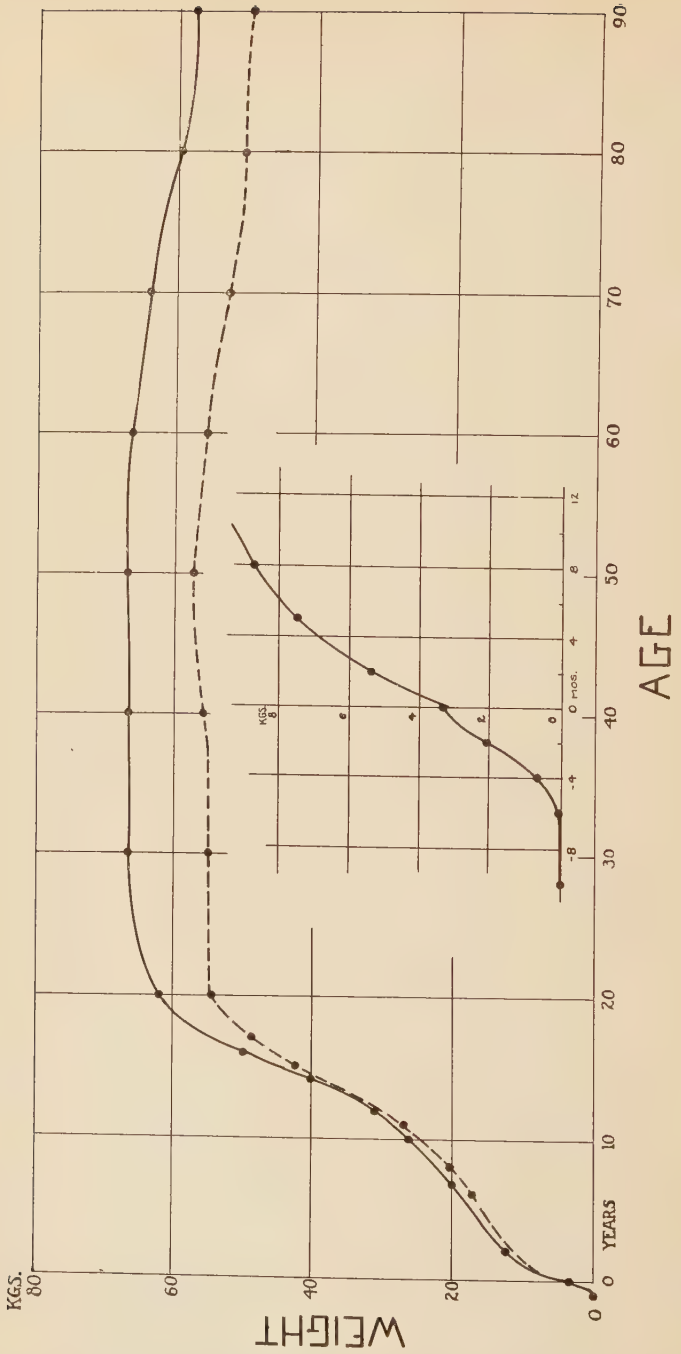

FIG. 133.—Curves showing average weights at each age in man. Solid line, male; dotted line, female. Inset gives curve for prenatal period and first postnatal year on a larger scale.

Growth is succeeded by a period of maturity in which the majority of tissues maintain the *status quo*, carrying on basic and functional metabolism in accordance with their inherent capacity, subject to such modifications in detail as are induced by changes in their environment.

As maturity advances senescence begins to be foreshadowed; the first manifestations consist in a lessening of plasticity; the readiness with which the cells respond to environmental changes declines. As individual tissues thus become less efficient, as the nervous system, the endocrine glands, the heart and bloodvessels, the alimentary organs or the kidneys function less well, other tissues, which might of themselves continue reasonably effective, suffer impairment of their environment through the partial failure of those tissues which have become senescent; thus they in turn have their capacities reduced, and the body as a whole pays the penalty for the senility of only a part of it. Very little is known as to the fundamental character of senescence. In the view of Child, it is the inevitable result of a progressive decline in the level of basic metabolism (page 65), but why metabolism declines as age advances remains to be determined.

Actual death from old age is rare. In the overwhelming majority of cases accident or disease disorganizes the complex bodily mechanism beyond its capacity to continue functioning. Assuming neither accident nor disease to be suffered, the advance of senescence nevertheless results inevitably in death, through failure of some vital mechanism to play its necessary part. Whatever the ultimate cause, the immediate crisis is marked by circulatory breakdown. The body as a whole is considered to be alive so long as the heart continues beating. The death point of individual tissues is the moment when the protoplasm settles irreversibly into a condition of stable equilibrium (page 33). This latter state is usually the result of anoxemia following the circulatory crisis (page 222).

Summary.

The germinal tissues are localized in the *ovaries* in females, in the *testes* in the male. All true germ cells pass through a process of maturation, whereby single chromosomes replace chromosome pairs in mature ova and spermatozoa.

By the process of *fertilization* (the entry of a sperm into an ovum) the characteristic number of chromosome pairs is restored. The physico-chemical equilibrium prevailing in the ovum is also upset, initiating the first cell division. The remainder of the process of development follows automatically provided suitable cell environment is maintained at every stage.

The *study of reproduction* from the physiological standpoint concerns itself with the conditions under which mature ova and spermatozoa are produced; the method by which these are brought together to secure fertilization; and the subsequent provision of suitable environment for the developing organism.

Puberty is the period at which sexual maturity is attained. It is marked by rapid development of the germinal tissues and the accessory organs of reproduction and by appearance of the secondary sexual characters.

The *immediate stimulus* to the bodily changes characteristic of puberty is hormonal. The source of the hormone is in the interstitial cells (also follicular epithelium in females). The more remote stimulus by which these cells are caused to become active at the particular time at which they do is not well established. Evidence suggests hormones from the pituitary and pineal bodies as possible factors.

Spermatozoa are produced in great numbers; continuously in man and most domestic animals, seasonally in many wild species. They have marked vitality and are actively motile. They accumulate in the seminal vesicles and adjacent tubes, where secretions from the accessory reproductive glands are added to make up the seminal fluid.

Insemination involves erection, intromission and ejaculation, the two latter constituting the male act in *coitus*. Erection is a vascular phenomenon, ordinarily induced reflexly. A center in the lumbar cord is postulated as the "coitus center." Erectile reflexes are mediated through this center, as are also the reflexes of coitus. Sexual excitement reinforces the reflex mechanism, insuring the performance of this biologically essential act.

The spermatozoa propel themselves *against the ciliary current* through the uterus and along the Fallopian tubes, toward the distal ends of the latter.

Ovogenesis, with attending formation of Graafian follicles, appears to occur continuously from an early embryonic stage to the menopause. Prior to puberty follicles degenerate and disappear as fast as formed, keeping the total number in the ovary constant. After puberty the same fate befalls most follicles, but a small percentage enlarge and persist for a longer time.

Ovulation is initiated by further enlargement of one or more follicles, due for the most part to increase in quantity of follicular liquid. The enlarged follicles then burst (in cats, rabbits and ferrets only in case of coitus) releasing the ova to be picked up by the Fallopian tubes and propelled along them by ciliary action toward the uterus. The passage requires three days in most forms.

Ovulation in most mammals, but not in man, is attended by

definite external signs, including sexual excitement; the period is designated as *œstrus*, and is the only time at which impregnation occurs in such forms as show it. The stimulus to ovulation and œstrus is chemical, being mediated by a hormone produced in the Graafian follicles.

Subsequent to ovulation the ruptured follicle is replaced by the *corpus luteum* (the replacement is in effect the assumption of new functions by cells already present). Among the functions of the corpus luteum is the production of a hormone inhibitory to ovulation. Hence, the latter cannot recur until degeneration of the corpus luteum takes place.

Under the influence of hormones produced at first by the maturing follicles and subsequently by the corpus luteum, the mucosa of the uterus undergoes changes preliminary to *implantation* of the embryo and to *placentation*. Whether pregnancy occurs or not the corpus luteum persists long enough for the preparatory uterine changes to go to completion. In the absence of pregnancy luteal degeneration occurs, followed by reversion of the uterus to its resting state. The period of luteal activity in non-pregnant organisms is known as *pseudo-pregnancy*, or the *progestational stage*.

In human (and other primate) females the preparatory uterine changes proceed to a stage of incipient hemorrhage; in the absence of pregnancy the climax is reached in about twelve days, when hemorrhage becomes pronounced, constituting the *menstrual flow*. Luteal degeneration then sets in and sloughing of uterine mucosal tissue takes place, resulting in return of the uterus to the resting state.

The human corpus luteum secretes a hormone similar to follicular hormone, in that it is effective in producing œstrus in lower animals. Human females are thus unique, so far as known, in the practically continuous production of a hormone with this property. The absence of *periodic œstrus* is conceivably related to this fact.

In the human species coitus is not definitely correlated with ovulation. Consequently, the occurrence of *conception* frequently depends on the survival power of the spermatozoa. It is somewhat doubtful whether these structures survive menstruation. If insemination occurs immediately following a period, however, they ordinarily persist long enough to be present at the succeeding ovulation.

Fertilization of the ovum occurs most frequently in a Fallopian tube; consequently development of the embryo has usually proceeded as far as the morula when it arrives at the uterus. *Implantation* depends on the presence of the embryo in contact with a specially prepared uterine wall. The stimulus to *placentation* is the purely mechanical contact of embryo, or other source of irritation, with the progestational uterus.

The fetus elaborates a hormone by which the functional life of the corpus luteum is prolonged throughout the *period of gestation*. Recurrence of ovulation is thus prevented.

During gestation the fetus is nourished by interchanges between its own blood and the maternal blood. These interchanges take place in the *placenta*. They involve passage of all materials concerned through membranes.

As the fetus reaches "term" retrogression of the corpus luteum sets in. *Parturition* is precipitated at this time (in women about two hundred and sixty-four days after fruitful ovulation) presumably as a result of luteal degeneration. The actual stimulus to uterine contraction is looked on as afforded by postpituitary hormone in increased amount. The relation between luteal degeneration and heightened postpituitary activity remains to be worked out.

Active corpus luteum produces a hormone that stimulates the *mammary glands* to functional development. This occurs more or less extensively at each pseudo-pregnancy, but rarely goes to completion except in true pregnancy. The beginning of active *lactation* usually coincides nearly with parturition. The first secretion is *colostrum*, a fluid differing somewhat from milk in composition. The production of true milk ordinarily begins in two or three days.

The only known essential to continued lactation after it is once started is periodic withdrawal of the accumulated store of milk. The mammary glands are looked on as modified sebaceous glands; they accordingly secrete continuously up to the capacity of their lacunæ. Overdistention of an alveolus results in less milk formation by the cells surrounding it. Continued overdistention causes the cells to cease functioning and to revert to their resting state.

The *menopause* marks the termination of reproductive capacity in women. The primary phenomenon is degeneration of the ovaries. Ovogenesis ceases, consequently neither Graafian follicles nor corpora lutea are produced. All bodily functions dependent on continued production of ovarian hormones are discontinued. Unsettlement of the autonomic system is usually more or less pronounced during the period.

The *life cycle* includes periods of growth, maturity and senescence and terminates in death. *Growth* is characterized by special growth metabolism, *maturity* by the maintenance of the *status quo*, *senescence* by a progressive lessening of plasticity; a decline in the facility with which cells perform their normal functions. *Death* may result from accident, disease or advancing senescence. In any event the complex bodily mechanism becomes disorganized beyond its capacity to continue functioning. The immediate crisis is marked by circulatory breakdown; individual tissue death by the settling of the protoplasm into an irreversible stable equilibrium.

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INDEX.

A

Aberration, monochromatic, 607
spherical, 607
Absorption from colon, 425, 431
from distal colon, 427
from stomach, 405, 409
Acapnia, 232, 241
Acclimatization, 224, 228
Accommodation, 608
amplitude of, 611
as a clue to distance, 674
region of, 611
Aceto-acetic acid, 234
Acetone, 234
Achromatic colors, 635
Acid, aceto-acetic, 234
amino-, 18, 181, 191
benzoic, 148
fatty, desaturation of, 186, 192
fixed, elimination of, 165
glutamic, 50
hippuric, 148
hydrochloric, secretion of, 141, 151
lactic, in muscle, 83
nucleic, 41
of bile, 414
of gastric juice, 398, 408
uric, 236
Acidosis, 167, 171
Acromegaly, 207, 212
Action current, 71
in nerve, 105, 117
"Active" molecules, 48
Acuity, visual, 606
Adaptation, 491, 497
in eye, 620, 637, 652, 684
of smell, 542, 545
of temperature receptors, 515, 533
of touch, 524, 533
Addison's disease, 209
Adjustment, external, 473
Adrenal bodies, 201
cortex, 208, 213
secretion, control of, 202, 211
Adrenin, function of, 201, 211
glycemia, 179, 190
Adsorption, 36
Affective states, 734, 743
in relation to autonomic system, 735, 743
Affective tone, 482, 493
of sensations, 493
Afferent neurons, 104
tracts of body sense, 706, 715
of hearing, 708, 715
of smell, 710, 715
of taste, 709
of vision, 708, 715
After images, 645, 684
sensation, 490
Agglutination, 255, 266
Agraphia, 729
Air, alveolar. *See* Alveolar air.
complemental, 367, 371
currents in nasal cavity, 541
minimal, 382
residual, 367, 371
supplemental, 367, 371
tidal, 367, 371
Albumin, 251, 265
Alcohol, elimination of, 148
Alexia, 729
Alexin, 256
Alkali reserve, 167, 171
Alkalosis, 232, 241
Allantoin, 237
All-or-nothing property in heart, 95
in muscle, 85, 97
in nerve, 110, 118
Altitudes, effect of, on oxygen uptake, 223, 228
Alveolar air, 367
determinations, 369
pressure, high, 225, 228
low, 223
Alveoli, 364
Amboceptor, 252
Ametropia, 613
Amino-acids, 18, 181, 191
Ammonia, 235, 242
Ammonium carbonate, 183
Amœboid movement, 78, 96
Ampholites, 26
Amplitude (sound), 548
Anaphylaxis, 256, 266
Anemia, 262, 268
Anaërobic metabolism, 50
Angle, visual, 606
Anoxemia, 221, 227
lung ventilation in, 377, 386
Antagonism of salts, 37

Anterior pituitary hormones, 207, 212
Antibody, 252, 265
Anticipatory reflex or reaction, 477, 495
Antidrome conduction, 334, 338
Antigen, 252, 265
Antiperistalsis in small intestine, 417, 423
Antiscorbutic vitamin, 195
Antithrombin, 276, 281
Antitoxin, 255, 266
Antrum pylori, 396
Aphasia, 728, 733
Aphemia, 729
Apnea, 370, 372
Appetite, relation of vitamin B to, 194
  secretion of gastric juice, 400, 408
Arachnoid villi, 359
Arborization, terminal, 101
Arterial pressure, 325, 338
    compensatory regulation of, 330
    determination of, 327, 328
    normal and abnormal, 329,338
    respiratory changes in, 353
Arteries, 286
Arterioles, 287
  functions of, 333
Artificial respiration, 379
Asphyxia, 378, 386
Aspiration of thorax, 383, 387
Association areas of cortex, 720
  fibers of cortex, 714, 716
Associative memory, 719, 731
Astigmatism, 616, 625
Astigmia, 616
Atrioventricular node, 292, 308
Atrium, 290, 312
Attention, 494
Auditory sensations, 555, 577
    duration of, 559
    fusion of, 560
    intensity of, 555
    localization of, 562, 577
    volume of, 559
Augmentation, theories of, 302
Augmentor center of heart, 299, 309
Auricle, 290
Auscultatory method, 328
Autointoxication, 426, 431
Automatisms, 726, 733
Autonomic centers, 131, 133
  nerves, distribution of, 130
  system, 128, 133
    function of, in affective states, 735, 743
Awareness, 731
Axis, optic, 599
Axon, 101
  reflexes, 338

B

Bacterial metabolism in small intestine, 419, 423
Bacteriolysis, 256
Basal metabolism, factors affecting, 461, 470
    in conditions of disturbed thyroid function, 462
    in fever, 462, 470
    measurement of, 456
    rate of, 456, 469
    relation of, to mass of protoplasm, 455, 469
      to surface, 454, 469
    significance of respiratory quotient in, 459
Base, elimination of, 166
Basement membrane, 135
Basophiles, 260
Bathmotropic effects, 301
Beats, 561
Behavior, factors in, 689, 697, 699
Benzoic acid, 148
Beri beri, 194, 210
Bile, 414, 423
  pigments, 240
  quantity of, 414
  salts, 414, 423
    circulation of, 415, 423
  secretion of, 414
Bilirubin, 240
Biliverdin, 240
Binocular perception of distance, 677, 687
  vision, 675, 686
Biological oxidation, 48, 57
Bios, 197, 210
Bitter taste, 537, 544
Blind spot, 631
Bladder, urinary, 441, 444
    innervation of, 442
Blood, as a physico-chemical system, 263
  buffer action of, 164, 170
  cells, 258, 266
  clotting, 273, 281
  defibrinated, 277
  distribution of, 272, 280
  plasma, 250, 265
  platelets, 263, 268
  quantity of, 269, 280
  reaction of, 166
  relation of, to cell environment, 246
  renewal of, in general, 247
  serum, 273
  transfusion, 279, 281
  volume of, 269, 280
    regulation of, 271, 280
Blood-flow, distribution of, 347
  in exercise, 349
  in traumatic shock, 350, 361
  velocity of, 321, 324
Blood-pressure, arterial. *See* Arterial pressure
  determination by manometer, 315

Blood-pressure, effect of, on urine volume, 438, 444
Body, ciliary, 585
sense, 702
afferent tracts of, 706, 715
surface, 455, 469
temperature, 156, 168
Bone, composition of, 230
Botulism, 427
Brain, 121, 132
circulation through, 351, 361
stem, afferent tracts in, 706, 716
Breathing, 365, 371
regulation of, 373, 385
types of, 370, 372
Brightness, 590
Brilliance, 634, 636, 684
discrimination of, 648, 684
Broca's convolution, 729
Bronchial tree, 364
Brownian movement, 30, 33
Buffer action, 162, 170
of blood, 164, 170
Bulb (eye), 583

C

Caffeine, 238
Caisson disease, 225
Calcium, in the body, 174, 189
metabolism of, 200, 211
in lactation, 174, 189
salts in bone, 230
Calorimetry, direct, 456, 469
indirect, 457, 470
Canals, semicircular, 504
Candle, international, 590
Capillaries, 287, 341, 360
effect of histamine on, 342
various reactions of, 342
Capillary capacity, 289
pressure, 286, 342, 360
Capsule, Bowman's 143, 151
function of, 144, 151
of lens, 586
of Tenon, 582
Carbohydrate, energy value of, 459
in muscle, 89
metabolism of, 176, 190
Carbon dioxide as metabolite, 231, 241
excess, 233, 242
monoxide, 222, 227
Cardiac centers, action of, 303, 310
cycle, 311, 323
muscle, 94, 98
sphincter of stomach, 393, 408
Cardio-augmentor center, 299, 309
Cardio-inhibitory center, 299, 309
Catalase, 51
Catalysis, 54
Cathode, physiological, 72
Cell environment, 153
Cell environment, factors in, 154, 168
maintenance of, in vertebrates, 245
membrane, 35, 37, 43
Cells, 35, 43
gustatory, 536, 544
hair, 570, 576
nerve, 100
olfactory, 539, 544
structure of, 40
Center, cardio-augmentor, 299, 309
cardio-inhibitory, 299, 309
respiratory, 374, 385
vasoconstrictor, 334, 339
vasodilator, 337, 339
Centers, autonomic, 131, 133
"vital," 131
Central nervous system, 121, 132
Cephalin, 20, 275
Cerebellar tracts, 704, 715
Cerebellum, connections of, 696, 716
function of, 695, 698
Cerebrospinal fluid, 359, 362
Cerebrum, cortex of, 700, 714
mass of, 700
projection fibers of, 702, 715
white matter of, 702, 715
Chain reflexes, 479
Check ligaments, 583
Chemical stimulation, sensations from, 535, 544
Chemotaxis, 116, 259
Chiasma, optic, 708
Chlorophyll, 52
Chloroplasts, 43
Choice, 699, 714
Cholesterol, 20, 35, 37, 209, 235, 242
Cholin, 20
Chondrioclasts, 230
Chordæ tendinæ, 313
Chorioid, 585
Choroid plexus, 359
Chromaffin tissue, 201, 211
Chromatic colors, 635
Chromatin, 42
Chromaticity, 649, 684
relation of, to state of retina, 651, 685
Chromosomes, 41, 745, 763
Chronaxie, 73
Chronotropic effects, 301
Churning in small intestine, 417, 423
Chyle, 421
Chyme, 411, 422
Cilia, 78, 96
Ciliary body, 585
muscle, 585, 609
processes, 585
Circle of Willis, 351
Circles, blur, 608
diffusion, 608
Circulation, effect of, on urine volume, 438, 444

Circulation, portal, 354, 361
pulmonary, 352, 361
velocity of, 353
through brain, 351, 361
kidneys, 355, 362
time, 320, 324
pulmonary, 354
velocity of, 321, 324
volume, 283, 308
determination of, 283
influence of posture on, 318
Clasmatocytes, 258
Clearness, 482, 494, 496
Clotting, details of, 274
in vivo, 278
methods of preventing, 277, 281
time, factors affecting, 274
Coagulation of blood. *See* Clotting.
Cochlea, functions of, 569, 578
Cochlear duct, 569
Coitus, 750, 764
center, 750, 764
Cold receptors, 532
spots, 480, 512, 532
"Cold sweat," 450, 452
Collaterals, 104
Colloid, 21
Colon, 425
bacterial action in, 426, 431
distal, absorption from, 427, 431
movements of, 428, 431
proximal, absorption of water from, 425, 431
movements of, 425, 430
Color, achromatic, 635
attributes of, 634
blindness, 656, 685
chromatic, 635
fields of retina, 652
hypotheses, 657
mixing, 654, 685
saturation of, 635
Colostrum, 760, 766
Commissural fibers of cortex, 714, 716
Common chemical receptors, 481
sense, 535, 544
Compensatory pause, 294, 309
Complement, 256, 266
Complemental air, 367, 371
Complementary colors, 650
Complex tones, 559
Concept as factor in behavior, 722
defined, 719, 732
Conception, 757, 765
Conditioned reflexes, 723, 732
Conduction, a property of protoplasm, 100
antidrome, 334, 338
bone, 554
criteria of, 105
Cones, function of, 643
of retina, 586
Cones of retina, number of, 631
Conoid of Sturm, 617
Consciousness, 482, 731
Constipation, 429, 431
Contact receptors, 480, 496, 532
Consummatory reflex, 477, 495
Contraction, isometric, 82, 97
isotonic, 82, 97
stages in, 80
Contrast, 647, 653, 684
Convoluted tubules, functions of, 145, 151
Cord, spinal. *See* Spinal cord.
Cornea, 583, 603
Corpus luteum, 754, 765
Corpuscles, Meissner's, 522
of blood, 258, 266
Pacinian, 501
red. *See* Red corpuscles.
tactile, 522, 533
Cortex, association areas of, 720
fibers of, 714, 715
commissural fibers of, 714, 716
efferent tracts from, 712, 716
inhibition from, 730
motor areas of, 712, 716
sensory areas of, 710
Corti, organ of, 569, 570, 571
Coughing, 382
Creatine, 238, 243
elimination, 239
Creatinine, 238, 243
Cretinism, 200
Crista acoustica, 504
Crystalline lens, 586, 604
Current of action, 71
of injury, 72, 77
Curvature of wave front, 596
Cutaneous pain, 528
receptors, 481, 511, 532
Cystein, 50
Cytolysis, 255, 266
Cytoplasm, 42

D

Dead space, 367, 372
Deafness, 568
Deaminization, 182, 191
Death, 763, 766
Decerebrate rigidity, 695, 698
Decompression, 225
Decortication, 720, 731
Defecation, 428, 431
Defects, focal, 608, 613
optical, 607
Defibrinated blood, 277
Deformation of skin, 523
Degeneration, Wallerian, 115
Deglutition, 392, 408
inhibition of, 395
Dehydration synthesis, 52, 57

Dendrites, 101
Dendron, 104, 117
Depressor influences, 335, 339
nerve, 306, 310, 335
Desaturation of fatty acids, 186, 192
Development, factors in, 747
Dextrin, 392
Diabetes insipidus, 146, 206, 438, 444
mellitus, 180
Diaphragm, action of, in breathing, 365, 371
Diastalsis, 397
Diastase, pancreatic, 413, 422
salivary, 392, 407
Diastasis, 312, 323
Diastole, 312, 323
Diastolic pressure, 326, 338
Diet, accessories of, 465
acid-forming and base-forming, 465
requisites of, 464, 470
Dietaries, practical, 467, 471
Difference threshold, 491
Digestion, 388, 407
Dilator of iris, 585, 619
Diopter, 602
Dioptry, 602
Diplopia, 676, 687
Direction eye, 581
visual perception of, 661, 685
Discus proligerus, 752
Dissociation constant, 162
electrolytic, 23
Distance receptors, 480, 496, 532
in relation to brain, 699, 714
visual perception of, 674, 677, 686
Diuresis, 440, 444
Donnan equilibrium, 27, 32, 33
Dromotropic effects, 301
Duct, cochlear, 569
Stenson's, 389
Duodenal cap, 404
Duplicity theory, 643, 684
Duration of hearing, 559, 577
of sensation, 482, 486, 489, 496
Dyspnea, 371, 372
mechanism of, 376, 386

E

Ear, middle, 552
ossicles of, 553
structure of, 551, 576
Edema, 358, 362
Effectors, 103
Effort, sense of, 736, 743
Ejaculation, 750, 764
Electrocardiograms, 296, 309
Emergency reaction, 179, 190, 203, 212
Emmetropia, 613
Emotions, 734, 743
in relation to autonomic system, 735, 743
Emulsoid, 21, 33
End bulbs, articular, 501
of Krause, 532
Endocrine glands, 149, 152, 197, 210
interrelations among, 209
Endolymph, 569, 576
Endolysin, 259, 267
Energy on micellar surfaces, 29
units, 454, 469
Enterokinase, 412, 419
Enzymes, 53, 58
formation of, from zymogen, 140
gastric, 398
intestinal, 419, 423
inverting, 419, 423
pancreatic, 412
salivary, 391
Eosinophiles, 260, 267
Epinephrin. *See* Adrenin.
Erection, 750, 764
Erepsin, 419, 423
Erythroblasts, 261, 267
Erythrocytes, 261, 267
Esophoria, 681
Esotropia, 681
Eupnea, 370, 372
Excitation, 69, 76
methods of, 72
Excitatory process in nerve, 105, 117
Excretion, organs of, 432
Exercise, blood-flow in, 349
lung ventilation in, 376, 386
Exophoria, 682
Exotropia, 681
Extensity, 482, 492, 496
External auditory meatus, 551, 576
secretion, 134, 149
Exteroceptors, 480, 496, 511, 532
Extrasystole, 294, 309
Eye, 622
accessory structures of, 623
adaptation in, 637, 652
development of, 587
movements, 664, 685
pursuit, 669, 686
saccadic, 669, 686
types of, 669, 686
muscles, action of, 666
paralysis of, 681, 687
nutrition of, 588
optical defects of, 624
perception of position of, 672
reduced, 605
refractive surfaces of, 623
schematic, 605
structure of, 581

F

Fallopian tube, 753, 765
Far point, 611, 616
Fascia bulbi, 582

Fat, conversion of, to carbohydrate, 88, 188
energy value of, 459
metabolism of, 185, 191
mobilization of, 188
orbital, 582
saponification of, 413
Fatigue, 487
effect of, on work yield, 463
nervous, 736, 743
recovery from, 737, 743
of muscle, 90, 97
of sensations, 487, 496
Fat metabolism, control of, 186, 191
in lactation, 187, 192
Fatty acids, desaturation of, 186, 192
Fenestra cochleæ, 570
vestibuli, 570
Fermentation in small intestine, 419, 423
Fertilization, 746, 763
Fever, 451, 453
metabolism in, 462, 470
Fiber, skeletal muscle, 79, 96
Fibrillation, cardiac, 294, 309
Fibrils of muscle, 80, 96
Fibrin, 273, 281
Fibrinogen, 252, 265
Fibrous tunic, 583
Fistula, esophageal, 400
gastric, 399
Thiry-Vella, 419
Fixation, field of, 665, 666
Fixed acids, elimination of, 165
Flicker, 647
Fluid, cerebrospinal, 359, 362
Flutter, cardiac, 294, 309
Flux, luminous, 590
Focal point, 600
Focus, depth of, 608
Follicle, Graafian, 751, 764
Fontana, spaces of, 588
Food poisoning, 426, 431
Foot candle, 590
Form, visual perception of, 673, 686
Fovea centralis, 628, 683
Frequency (sound), 548
Fresnel, 590
Function, control of, 69
Functional metabolism, 65, 67
Fundamental, frequency of, 548
Fundus of stomach, 396
Fusion of hearing, 560
of visual sensations, 647, 684

G

Gall-bladder, function of, 415
Gall-stones, 235, 242
Ganglia, parasympathetic, 129
sympathetic, 129, 133
Ganglion, spiral, 571
Gastric cycle, 397
Gastric juice, 397, 408
quantity of, 401, 408
secretion of, 399, 401
motility, 397
Gastrin, 402, 409
Genes, 41
Germinal tissues, 745, 763
Gestation, 757, 766
period of, 759, 766
Gigantism, 207, 212
Gland action, mechanics of, 136, 150
cell metabolism, 137, 150
Glands, 134
endocrine, 149, 152, 192, 210
interrelations among, 209
intestinal, 418
mammary, 759, 766
of Bowman, 539
parathyroid, 200
puberty, 749
salivary, 389, 407
sebaceous, 148, 152
structure of, 135
sweat, 142, 151, 449
tear, 142, 151
thyroid, 198
Glare, 639
Glaucoma, 588
Globin, 215
Globulin, 251, 265
Glomerulus, 143, 151
Glucose, concentration in blood, 176, 190
mobilization of, 178, 190
tolerance, 177, 190
Glomerular filtration, 433, 443
Glutamic acid, 50
Glutathione, 50, 57
Glycemia, 176, 190
adrenin, 179, 190
nervous, 178, 190
Glycogen, 79, 89
in liver, 177, 190
Glycogenase, 178, 190
Glycosuria, 176, 190
phlorhizin, 179, 190
Goiter, endemic, 200
exophthalmic, 199
Gout, 237
Graafian follicle, 751, 764
Granulocytes, 258
Gravity, effect of, on circulation, 345
Growth curves, human, 762
inhibitors, 64
in vitro, 63
metabolism of, 61, 66
periods of, 62
Gustatory cells, 536

H

Habits, 726, 733
Hair cells, 570, 576

Hair cells, nerve supply of, 522
olfactory, 539, 544
tactile, 522
Hearing, 546
afferent tract of, 708, 715
Ewald's non-resonance hypothesis of, 573, 578
Helmholtz's resonance hypothesis, 572, 578
hypotheses of, 572
non-resonance frequency hypotheses of, 573, 575
number of sensations in, 574
reactions from, 554, 576
receptor for, 551, 576
relation of, to speech, 568
sensations of, 555, 559, 560, 562, 577
threshold of, 555, 577
Heart, 290, 308
augmentation of, 299, 309
beat, initiation of, 293, 309
block, 295, 309
centers, 303, 310
conducting system of, 293, 308
conduction of excitation in, 96, 99
cycle of, 311, 323
factors in output of, 318, 323
flutter and fibrillation of, 294, 309
inhibition of, 299, 309
muscle, influence of salts on, 95
nervous regulation of, 299, 309
output of, 318
pacemakers of, 292, 308
refractory period of, 95, 98, 293, 309
sounds, 317, 323
valves, 313, 323
action of, 315
work of, 320, 323
Heat center, 446, 452
transfer in body, 446, 451
Helium, use of, in diving, 226
Helmholtz double layer, 23, 27
Hem, 215
Hematopoietic tissue, 261, 267
Hemochromogen, 215
Hemoglobin, 215, 226
Hemolysis, 256
Hemophilia, 278, 281
Hemorrhage, effect of, on blood volume, 272
lung ventilation in, 378, 386
Henry's law, 214, 226
Heparin, 275, 281
Herpes zoster, 342
Heterophoria, 681
Heterotropia, 681
Hexose phosphate, 84, 89, 96
Hibernation, 155
metabolism in, 189
Hippuric acid, 148
Hirudin, 276
Histamine, 342, 360
His-Tawara bundle, 293, 308
Histiocytes, 258
Homothermous animals, 446, 451
Hormones, 55, 58, 149, 197, 210
reproductive, relation of, to metabolism, 208
Hot sensation, 517
Hues, 649, 684
number distinguishable, 650, 685
Humor, aqueous, 587, 589, 604
vitreous, 586
Humoral influences, 132
Hunger, 393
Hydrocephalus, 359
Hydrochloric acid, secretion of, 141, 151
Hydrogen acceptors, 49, 57
transporters, 49, 57
Hydrogen-ion concentration, 24
a factor in cell environment, 160, 169
Hydrolysis, 52, 57
Hydrostatic test, 382
Hypercalcemia, 201, 211
Hyperglycemia, 176, 178, 179, 190
Hyperopia, 613, 625
Hyperphoria, 682
Hyperpituitarism, 207
Hyperpnea, 370, 372
mechanism of, 375, 385
Hypertension, 329, 338
Hyperthyroidism, 199, 211
metabolism in, 462
Hypertonic solution, 32
Hypertropia, 681
Hypophysis, 204
Hypopituitarism, 207
Hypotension, 329, 338
Hypothyroidism, 200, 211
metabolism in, 462
Hypotonic solution, 32
Hypoxanthin, 237

I

Illumination, 590
Illusion, sensory, 719, 731
Image formation, 579, 590, 603
forming eye, 581
Immunity, 252, 265
artificial, 253
Immunization process, 253
Implantation of ovum, 757, 765
Impulse, nervous, 106, 117
Inanition, 468, 471
Incisura angularis, 396
Incus, 553
Index of refraction, 596
Indifferent temperature, 515, 533
Induction shocks, 73
Inhibition, 75

Inhibition, cortical, 730
theories of, 302
Inhibitory center of heart, 299, 309
Injury current, 72, 77
Innervation of muscle, reciprocal, 693, 698
selective, 690, 697
sense, 501
Inotropic effects, 301
Insemination, 750, 764
Insulin, 203, 212
and blood sugar, 178, 180, 190
excess of, 180, 190
relation of, to fat metabolism, 186
secretion, control of, 204, 212
Intensity of sensations, 482, 486, 490, 492, 496
auditory, 555, 558, 572, 574, 575, 577
taste, 539
temperature, 533
touch, 524
Internal capsule, 712
secretion, 134, 149
Internuncial neurons, 104, 117
Interstitial tissue, 748, 764
Intestine, large, 425, 426, 427, 428, 430, 431
small, 416, 418, 419, 420, 423, 424
Intestinal juice, 418, 423
Intracardiac pressure, 314
Intracellular membranes, 40, 44
Intracranial pressure, 352
Intraocular pressure, 583, 588
Intrapulmonary pressure, 382, 387
Intrathoracic pressure, 383, 387
Intratracheal insufflation, 365
Intromission, 750, 764
Iodine in the body, 175, 189
Ions, orientation of, 38
Iris, 585, 619
innervation of, 625
Iron in the body, 175, 189
Irritability, 69, 76
Islands of Langerhans, 203, 212
Isoagglutinins, 280
Isoelectric point, 25
Isometric contraction, 82, 97
Isotonic contraction, 82, 97
solutions, 32

J

Jaundice, 415
Junctions, myoneural, 104, 112, 690, 697
recepto-neural, 104

K

Karyoplasm, 42
Katastalsis, 397
Ketone bodies, 234, 242
in relation to diet, 464, 471
Kidney, 432
cells, synthesis in, 147
circulation through, 355, 362
metabolism of, 147
tubule, 143, 151
Krause, end bulbs of, 512, 532
Kupffer cells, 258
Kymograph, 81

L

Labyrinth, loss of function of, 505
non-acoustic, 405, 499, 504, 509, 510
relation of, to tonus, 694, 698
sensations from, 508
stimulation of, 507
Lactase, 419, 423
Lactate, sodium, 88, 97, 234, 242
Lactation, 759, 766
fat metabolism in, 187, 192
relation of, to pregnancy, 761, 766
Lacteals, 421
Lactic acid in muscle, 83
Lambert, 590
Langerhans, islands of, 203, 212
Language, 727, 733
areas, 728
Large intestine, 425, 426, 427, 428, 430, 431
Larynx, 565
Lashes, eye, 583
Latent period, 81, 97
Learning, 721, 732
Lecithin, 20
Lemniscus, 707
Leukocytes, 258, 266
number of, 259, 266
Leukocytosis, 258, 266
Leukopenia, 258, 266
Lens, converging, 599
crystalline, 586, 604, 608
curvatures of surface of, 610
cylindrical, 617
diverging, 599
refractive power of, 603
Toric, 617
Lenses, 599
Lids, eye, 583
Ligaments, check, 583
suspensory, 586, 609
Light, 622
reflex of pupil, 620
refraction of, 623
relation of, to vitamin D, 196
Light-sensitive structures, comparative anatomy of, 580
Limen, 490
difference, 491
Lipase, 413, 423

Lipemia, 186, 192
Lipides in cell environment, 185, 191
Listing's law, 671
Liver, deaminization function of, 182, 191
glycogenic function of, 177, 190
urea formation in, 183, 191
Local excitatory process, 105, 117
sign, 485, 494
of touch, 526
Localization, 482, 485, 494, 496
of hearing, 562, 577
of touch, 525
Locomotion, 498
Lung, alveoli, 364
capacity, 367, 371
circulation through, 352, 361
ventilation, 365, 371
acid control of, 374, 385
in anoxemia, 377, 386
in exercise, 376, 386
in hemorrhage, 378, 386
nervous factors in, 375, 385
relation of, to metabolism, 369, 372
Lumen, 590
Lux, 590
Lymph flow, 357, 362
Lymphagogues, 358, 362
Lymphatics, 357, 362
Lymphocytes, 260, 267

M

Macrophage, 260, 267
Macula lutea, 504, 628, 683
Malleus, 553
Malpighian body, 144
Maltase, 419, 423
Maltose, 392
Mammary glands, 759, 766
Manometer, 315
Masking of tones, 562, 574, 577
Mastication, 389, 407
Maturation, 745, 763
Maturity, attainment of, 746
characteristics of, 763, 766
Meal, character of, 389
Meatus, external auditory, 551
Mechanical stimulation of skin, 518
Megacaryocytes, 263
Meissner's corpuscles, 522
Melanin, 209
Melanophores, 206
Membrane, basilar, 570
cell, 35, 37, 43
intracellular, 40, 44
nuclear, 42
permeability, 70
semipermeable, 30
tectorial, 571
tympanic, 552
Memory, 717, 731
associative, 719, 731
Menopause, 766
Menstruation, 755, 765
Metabolism, 46, 57
anaërobic, 50
basal, 60, 66
basic, 59, 66
characteristics of, 245
data, significance of, 454
effect of exercise on, 463
functional, 65, 67
in fever, 462, 470
in hibernation, 189
in nerve, 107
maximal, 463
measurements, 456, 470
of calcium, 174, 189, 200, 211
of carbohydrate, 176, 190
of fats, 185, 191
control of, 186, 191
of glands, 137, 150
of growth, 61, 66
of kidney, 147
of protein, 181, 191
reactions of, 47
relation of lung ventilation to, 369, 372
summarized, 56
total, 462
water of, 157, 169
Metabolites as factors influencing metabolism, 229
insoluble, 229, 241
nitrogenous, 235, 242
non-nitrogenous, 231
Metathrombin, 276, 281
Meter candle, 590
Methyl purins, 238
Mett's tubes, 402, 409
Micellæ, 21, 33, 37
hydrogen-ion concentration a factor in, 26
orientation in, 23, 33
role of salts in, 24
Microphage, 259, 267
Micturition, 441, 444
nervous control of, 442
Millilambert, 590
Millimicron, 590
Milliphot, 590
Mind in relation to physiology, 717, 731
Minimal air, 382
Minuthesis, 486, 496
Mitochondria, 43
Mobilization of fat, 188
Modality, 485
Molecules, "active," 48
non-polar, 22
polar, 22, 26
Monocular judgments of distance, 674, 686
parallax, 674

Monocytes, 260, 267
Motion, ciliary, 78, 96
visual perception of, 673, 686
Motoceptors, 495, 499, 509
reflexes from, 502
sensations from, 502
structure of, 501
Motor neurons, 104, 117
distribution of, 690, 697
Mouth, watering of, 391
Movement, amœboid, 78, 96
sensation of, 502
Mucin, 139, 149
Mucinogen, 139, 150
Mucous cells, 138, 149
Muscle, a chemical engine, 83, 96
action, stages, in, 80, 96
cardiac, 94, 98
ciliary, 585, 609
fatigue of, 90, 97
ocular, 582
of eye, action of, 666
pattern, 479
relaxation of, 86
respiratory, 366, 371
selective innervation of, 690, 697
sense, 495
receptors, 495, 499, 501, 502, 509
skeletal, 79, 96
smooth, 92, 98
spindle, 500, 509
tensor tympani, 553
Musculo-tendinous organs of Golgi, 501
Myelocytes, 260, 267
Myenteric reflex, 394, 403, 408
Myoneural junctions, 104, 112, 690, 697
Myopia, 613, 625
Myotatic reflex, 691, 697
Myxedema, 200

N

Narcotics, effect of, on nerve, 110
relation of, to membrane permeability, 38
Nausea, 417, 423
Near point, 611, 616
Nerve, action current in, 105, 117
all-or-nothing property in, 110, 118
cell, 100
functions of, 115, 119
depressor, 306, 310
effect of narcosis on, 110
endings, free intra-epithelial, 528, 534
impulse, 106, 117
velocity of, 109, 118
metabolism in, 107
net, 100, 116
optic, 585
propagated disturbance in, 109, 117
Nerve, refractory period in, 106
rings of hair follicles, 533
specific energy of, 484
temperature coefficient in, 109
trunks, 121, 132
energy to stimulate, 474
Nervous fatigue, 643, 736
recovery from, 737, 743
system, 120
Neuron, 101,117
afferent, 104
connections of, 122
internuncial, 104, 117
motor, 104, 117
postganglionic, 129, 133
preganglionic, 129, 133
receptive, 104, 117
Neutrality preserving mechanism, 161, 165, 169
Neutrophiles, 258
Nitrogen equilibrium, 465, 471
uptake of, at high pressure, 225
Nitrogenous metabolites, 235, 242
Nociceptors, 480, 496, 528
Nodal point, 599
Node (sound), 547
Nodes of heart, 292, 308
Nomogram, 264
Non-acoustic labyrinth, 495, 499, 504, 505, 509, 510, 694, 698
Non-polar molecules, 22
Nuclear membrane, 42
Nucleic acid, 41
Nucleoprotein, 41
Nucleus, 41, 44
Nutrients, 175, 189
equilibrium among, 187, 192
storage of, 188
Nystagmus, 505

O

Octave, 560
Odors, combining, 543
classification of, 541
localization of, 543
neutralizing, 543
Œstrus, 753, 765
Olfactory cells, 539, 544
hairs, 539, 544
receptors, 539, 544
Opsonin, 259, 267
Optic axis, 599
chiasma, 708
disk, 628
nerve, 585
papilla of, 628, 683
tract, 708
Ora serrata, 585, 627
Orbits, 582
Organ of Corti, 569, 576
Orientation in micellæ, 23, 33

Orthophoria, 681
Osmotic pressure, 30, 33
Ossicles, auditory, 553, 576
Osteoclasts, 230
Otoconia, 504
Otoliths, 504
Ovaries, 745, 763
Overtones, 549, 576
Overventilation, effects of, 379, 386
Ovogenesis, 751, 764
Ovulation, 752, 764
Ovum, implantation of, 757, 765
Oxidant, 48
Oxidation, biological, 48, 57
recovery, of muscle, 87
Oxidation-reduction potential, 48
reactions, 48
Oxygen, activation of, 51
caloric value of, 458
debt, 91, 98
effect of excessive amount of, 225
in tissue fluid, 214, 226
tension of, in solution, 214, 226
of tissuess, 220
transport in the active body, 219
in the resting body, 217
utilization, effect of altitude on, 223, 228
limit of, 221
Oxyhemoglobin, 215, 226
dissociation curve of, 216
Oxytocic action of postpituitary hormone, 205

P

Pacemakers of heart, 292, 308
Pacinian corpuscles, 501
Pain, 480, 519
cutaneous, 528
energy to arouse, 474
in deeper tissues, 530
receptors, 533
stimulation of, 529
referred, 532, 534
spots, 528, 534
Pancreatic diastase, 413, 422
juice, composition of, 412, 422
functions of, 412, 422
secretion of, 411
Papillæ, filiform, 538
foliate, 538, 544
fungiform, 538, 544
vallate, 538, 544
Parallax, monocular, 674
Paralysis of eye muscles, 681, 687
Parasympathetic nerves, distribution of, 130
system, 129, 133
action of, 131
Parathyrin, 200, 211
Parathyroid gland, hormone of, 200
Parotid gland, 389
Parthenogenesis, 746
Partials, 549
Parturition, 758, 766
Pattern, muscle, 479
stimulus, 479
Pepsin, 398, 408
Peptic action, measurement of, 402, 409
Peptone, 398
Perception, space, 494
visual, 673, 674, 676, 677, 686
Percepts, 718, 731
Perilymph, 554
Perimeter, 652
Period, latent, 81, 97
Peripheral nervous system, 121, 132
Peristalsis, 393, 416, 423
Peristaltic rush, 416, 423
Peroxidase, 51
Phagocytes, 258
Phase (sound), 547,
Phlorhizin glycosuria, 179, 190
Phorometer, 682
Phosphates, 234, 242
Phosphatides, 18, 20, 33, 35, 37
Phot, 590
Photosynthesis, 52
Physiological cathode, 72
systems, 247
Pigments, 240, 243
Pineal body, 207, 212
Pinna, 551, 576
Piqûre, 178, 190
Pitch, 555, 558, 572, 574, 576, 577
audible range of, 548, 556
Pituitary body, anterior lobe of, 206, 212
posterior lobe of, 204
Placenta, 758, 766
Placentation, 758, 765
Plasma, 250, 265
proteins, 251, 265
Plastids, 43
Platelets, 263, 268
Plexus, choroid, 359
Pneumothorax, 384, 387
Polar molecules, 22, 26
Polycythemia, 262, 268
Polymorphonuclear cells, 258
Portal circulation, 354, 361
Position, sensations of, 502
Postganglionic neurons, 129, 133
Postpituitary hormone, 204, 214
action of, 205, 212
tartrate, 205
Postural reflexes, 478, 495
Posture, effect of, on venous pressure, 345, 361
influence of, on circulation volume, 318
maintenance of, 498, 508, 510
relation of tonus to, 693, 698
restoration of, 498
Potassium in the body, 174, 189

Potential, oxidation-reduction, 48
Precipitation in immunity, 254, 266
Precipitin, 255, 266
Precurrent reflex or reaction, 477, 495
Preganglionic neurons, 129, 133
Pregnancy, 757, 765
  extra-uterine, 753
Premature contraction, 294, 309
Prepyloric region of stomach, 398
Presbyopia, 618, 625
Pressor influences, 335, 339
Pressure, arterial, 325, 327, 328, 329, 330, 338, 353
  capillary, 342, 360
  cutaneous, 520
  diastolic, 326, 338
  intracardiac, 314
  intracranial, 352
  intraocular, 583, 588
  intrapulmonary, 382, 387
  intrathoracic, 383, 387
  osmotic, 30, 33
  sensation of, 502
  systolic, 326, 338
  venous, 344, 360
Processes, ciliary, 585
Progestational stage, 755, 765
Propagated disturbance, 109, 117
Proprioceptors, 480, 495, 498, 499, 509
Prosecretin, 411, 422
Proserozyme, 274
Protein, 18, 33, 35
  consumption, optimum, 466, 471
  dietary significance of, 464, 466
  energy value of, 459
  metabolism of, 181, 191
  of plasma, 251, 265
  "specific dynamic action" of, 461, 470
  storage, 181, 191
  utilization of, 181, 184, 191
  wastage, 60
Proteinates, 26
Proteoses, 64, 398
Prothrombin, 274, 281
Protoplasm, 17, 33
  a colloid, 21
  temperature limits of, 155, 168
Protoplasmic water, 158
Pseudoglobulin, 274
Pseudopregnancy, 755, 765
Ptyalin, 391
Puberty, 748, 764
  gland, 749
Pulmonary circulation, 352, 361
Pulse, 330, 339
  determinations, 332
  pressure, 326, 338
Pupil, 585
  area of, 620
  associated movements of, 622
  effect of drugs on, 626
  physiological size of, 620
Pupil, reactions of, 619
  size of, 619, 625
Pupillary size, 619, 625
Purin bodies, 236, 242
  exogenous and endogenous, 237
  methyl, 238
Purkinje's fibers, 632
  phenomenon, 642
Pursuit movements of eye, 669, 686
Putrefaction in colon, 426, 431
  in small intestine, 420, 423
Pyloric sphincter, 397
Pylorus, 396
Pyramids, 712, 716

Q

Quality of sensations, 484, 496

R

Rachitis, 196
Radiation, visible, 580, 590, 623
Ray of light, 591
Reaction, time of smell, 541, 545
  of taste, 539
Reactions, 476
  acquired, 721, 732
  anticipatory, 477, 495
  classification of, 476, 495
  consummatory, 477, 495
  eliminative, 477, 495
  food-getting, 477, 495
  locomotive, 478, 495
  of blood and tissues, 166
  of metabolism, 47
  oxidation-reduction, 48
  prehensive, 478, 495
  protective, 477, 495
  reproductive, 477, 495
  respiratory, 477, 495
  social, 479
  sound-producing, 478, 495
  temperature regulative, 477, 495
Reactivity, selective, 699, 714
Reasoning faculty, 721, 732
Receptaculum chyli, 358, 421
Receptive neurons, 104, 117
Recepto-neural junctions, 104
Receptors, 76, 103, 473, 495
  accessory structures of, 475
  adaptation in, 491, 497
  auditory, 496
  classification of, 479, 495
  common chemical, 481, 496
  contact, 480, 496, 511, 532
  cutaneous, 481, 511, 532
  distance, 480, 496, 511, 532
  for hearing, 551
  for smell, 539, 544

Receptors for taste, 536, 537, 544
for warmth, 496, 533
functional metabolism of, 487
of cold, 496
of cutaneous pain, 496
of muscle sense, 495, 499, 501, 502, 509
olfactory, 496
pain, 533
relation of, to reflex arc, 473
somatic, 480, 495
temperature, 512, 514, 515, 532, 533
touch, 480, 496, 533
visceral, 480, 496
Reciprocal innervation, 693, 698
Recovery oxidation, 87
Rectum, 429
Red corpuscles, 261, 267
hemoglobin content of, 262, 267
number of, 261, 267
origin and fate of, 261, 267
Reductant, 48
Reduction potential, 48
Referred pain, 532, 534
Reflection, 592
Reflex, 473, 476
action, 123, 132
anticipatory, 477, 495
arc, 120, 132, 474, 495
auditory, 554
axon, 338
chain, 479
complex, 125, 127, 133
conditioned, 723, 732
consummatory, 477, 495
from motorceptors, 502
initiated by taste, 539
labyrinthine, 505
light, of pupil, 620
myenteric, 394, 403, 408
myotatic, 691, 697
neck, 509
of deep pain, 531
of smell, 543
postural, 478, 495
precurrent, 477, 495
prepotent, 478
protective, 529, 534
receptive, 478
respiration, 381
salivary, 390
scratch, 520
simple, 120, 132
unconditioned, 723, 732
Refraction, 590, 593
index of, 596
Refractory period in nerve, 106
of heart, 95, 98, 293, 309
Relaxation of muscle, 86
Renal circulation, 355, 362
Rennin, 398, 408
Reproductive cycle in absence of pregnancy, 756
hormones, relation of, to metabolism, 208
Residual air, 367, 371
Respiration, 364
artificial, 379
Respiratory center, 374, 385
data, 381
muscles, 366, 371
quotient, 380, 386
relation of, to breathing, 380
significance of, in metabolism measurements, 459
reflexes, 381
Reticulo-endothelial cells, 258, 266
Retina, 585, 627
electromotive changes in, 633, 684
regional differences in, 628
resolving power of, 661, 685
rod-free area of, 628, 683
sensory gradient in, 670, 686
Retinal grain, 661
image, inversion of, 672
pigment, migration of, 632
rivalry, 683
Rheobase, 73
Rhodopsin, 632
Rhythmic segmentation, 417, 423
Rickets, 196
Rigidity, decerebrate, 695, 698
Rigor, 92, 98
Ringer's solution, 37
Rods, function of, 643
of retina, 586
number of, 631
Rouget cells, 287
Ruffini, corpuscles of, 512

S

Saccadic movements of eye, 669, 686
Saccule, 504
Sagitta, 598
Saliva, composition of, 390
function of, 391, 407
quantity of, 391
Salivary diastase, 392, 407
glands, 389, 407
reflexes, 390
secretion, control of, 390
relation of affective states to, 391
Salt antagonism, 37
Salts as factors in cell environment, 172, 189
of plasma, 250, 265
role of, in micellæ, 24
Salty taste, 537, 544
Sarcolemma, 79, 96
Sarcoplasm, 79, 96
Sarcostyles, 79, 96

Saturation of color, 650, 685
Scala tympani, 569
vestibuli, 569
Schlemm, canal of, 588
Sclera, 583
Scratch reflex, 520
Scurvy, 195
Sebaceous glands, 148, 152
Secretin, pancreatic, 411, 422
Secretion, control of, 136, 140, 150
external, 134, 149
internal, 134, 149
of urinary constituents, 434, 443
salivary, 390, 391
Secretory process, 135, 150
Segmentation, rhythmic, 417, 423
Selective reactivity, 699, 714
Semicircular canals, 504
Seminiferous tubules, 749
Senescence, 763, 766
Senility, 153
Sensations, 482
affective tone of, 493
attributes of, 482, 496
auditory, 555, 576
position in time of, 562
clearness of, 494
duration of, 486, 489
extensity of, 492
fatigue of, 487, 496
from chemical stimulation, 535, 544
from motoceptors, 502
intensity of, 486, 490
localization of, 494
of cold, 514
of deep pain, 531
of hearing, 555, 559, 560, 562, 577
of taste, 537, 538, 539, 544
of temperature, 516, 518, 533
of touch, 524, 525, 526, 533, 534
quality of, 484, 496
threshold of, 493
time relations of, to stimulation, 486
upper limit of, 493
visual, 634, 684
Senses, body, 702
modal, 485
Sensitivity, selective, 474, 495, 496, 528
Sensitization, 257
Sensory illusion, 719, 731
Serous cells, 138, 149
Serum, 273
albumin, 251, 265
globulin, 251, 265
Sexual characters, secondary, 748
Shock, anaphylactic, 256, 266
traumatic, 350, 361
Sign, local, 485, 494
Sinoatrial node, 292, 308
Sinus venosus, 292
Skeletal muscle, 79, 96
Skeletal muscle, autonomic innervation of, 692, 698
tonus of, 691, 697
Skin, mechanical stimulation of, 518, 533
physical situation in, 512
Sleep, 738, 744
bodily state in, 741, 744
metabolism in, 462, 470
Small intestine, absorption from, 420, 424
bacterial action in, 419, 423
fermentation in, 419, 423
innervation of, 418, 423
movements of, 416, 423
myenteric reflex in, 416
passage of chyme through, 416
putrefaction in, 420, 423
Smell, 535, 539
adaptation, 542, 545
afferent tract of, 710, 715
localizing power of, 543
reaction time of, 541
receptors, 539
reflexes from, 543
relation of breathing movements to, 541, 545
to taste, 543, 545
stimuli of, 540, 545
threshold of, 542, 545
Smooth muscle, 92, 98
innervation of, 129
Sneezing, 382
Sodium chloride in body, 172, 189
lactate, 88, 97, 234, 242
Solution, hypertonic, 32
hypotonic, 32
isotonic, 32
Somatoceptors, 480, 495
Sound, complex, 548, 576
physical nature of, 546, 576
simple, 547, 576
Sounds of heart, 317, 323
Sour taste, 537, 544
Space perception, 525
position in, 482, 494, 496
"Specific dynamic action" of nutrients, 461, 470
energy of nerves, 484
Speech, 565, 566, 568
center, 729
distribution of energy in, 567
relation of, to hearing, 568
Spermatozoa, 749, 764
numbers of, 749
Sphincter, cardiac, 393, 408
of iris, 585, 619
pyloric, 397
Sphygmograph, 332
Sphygmomanometer, 328
Sphynogomyelin, 20
Spinal cord, 121, 132
afferent paths of, 703, 715

Splanchnic area, 333
compensation in, 345, 361
Spots, cold, 532
pain, 534
touch, 533
warmth, 533
Squint, 681, 687
Stapes, 553
Starvation, 468, 471
Stenson's duct, 389
Statocyst, 507
Stereoscope, 679, 687
Sterility, relation of, to vitamin E, 197
Sterol, 193
Stimuli, classes of, 70, 76
Stimulus, 69, 76, 481, 488, 496
descrimination threshold of, 491, 497
effects of, 481
for smell, 540, 545
for taste, 537, 544
for temperature sensations, 515
for touch, 523
for vision, 580, 591
nature of, 487
of temperature receptors, 533
pattern, 479
subliminal, 490
tactile, 523
threshold, 490
time relations of, to sensation, 486
Stirrup, 553
Stomach, absorption from 405, 409
churning of food in, 396, 408
disposition of food in, 395, 408
emptying of, 403, 409
entry of food into, 394
innervation of, 393, 405, 409
musculature of, 393
prepyloric region of, 398
subdivisions of, 396
Storage of nutrients, 188
of protein, 181, 191
Strabismus, 681, 687
Stroke index, 318, 323
volume, 318, 323
Stromuhr, 286, 308
Strychnine, effects of, 125
Sturm, conoid of, 617
Subliminal stimulus, 490
Sublingual gland, 389
Submaxillary gland, 389
Succus entericus, 418
Sucrase, 419, 423
Sugar, mobilization of, 178, 190
Sulphates, 234, 242
Supplemental air, 367, 371
Supplementary secretion of gastric juice, 401, 409
Suprarenal bodies, 201
Surface energy, 29, 33, 36
of body, 455, 469
tension, 30
Swallowing, 392, 408
inhibition of, 395
Sweat, "cold," 450, 452
glands, 142, 151
nervous regulation of, 450
secretion, 449, 452
volumes of, 450
Sweet taste, 537, 544
Sympathetic discharge, effects of, 736
nerves, distribution of, 130
system, 129
action of, 131
Synapses, 103, 112, 117
fatigability of, 114, 119
susceptibility of, to anesthetics, 114, 119
to lack of oxygen, 114, 119
Synthesis, dehydration, 52, 57
Systems, physiological, 247
Systole, 312, 323
duration of, 312
Systolic pressure, 326, 338

T

Tactile corpuscle, 522, 533
stimulus, nature of, 523
Taste, 535, 536
afferent tract of, 709
buds, 481, 535, 536, 544
qualities, basis of, 538
receptors, 536
stimuli of, 537, 544
sensations, 537, 544
intensity of, 539
physiological basis of, 538, 544
reaction time for, 539, 544
reflexes from, 539
Taurin, 414
Tear glands, 142, 151
Tears, 583, 603
Temperature as a factor in cell environment, 154, 168
coefficient, 156
fall, prevention of, 448, 452
gradient in skin, 513, 533
indifferent, 515, 533
limits of protoplasm, 155, 168
of human body, 156, 168
optimum, 156
receptors, 512, 532
adaptation of, 515, 533
function of, 514, 533
regulation, 446, 451, 518, 533
artificial aids to, 448, 452
rise, physiological, 450, 452
prevention of, 449, 452
sensations, intensity of, 516
relation of, to temperature regulation, 518, 533
Tendon spindles, 501, 509
Tension development, 85, 97

Tension in smooth muscle, 93, 98
sensations of, 502
Test types, 607
Testes, 745, 763
Tetanus, 89, 97
Tetany, 233, 241
Theine, 238
Theobromine, 238
Thirst, 159
Thorax, aspiration of, 383, 387
Threshold, 493, 497
difference, 491, 497
for touch, 524
of hearing, 555, 577
of smell, 542, 545
of visibility, 638
stimulus, 490
two-point, 525, 527, 534
Thrombin, 274, 281
Thrombogen, 274
Thrombus, 274, 281
Thyroid function, aberrant, 199, 211
gland, hormone of, 198, 211
Thyroxin, 50, 57, 198, 211
Tickle, 519, 520
Tidal air, 367, 371
Timbre, 548, 559, 576, 577
Time, position in, 482, 494, 496
Tissues, reaction of, 166
Tolerance, upper limit of (hearing), 493, 556
Tone, affective, 482, 493, 496
islands, 573, 574
lacunæ, 573, 574
Tones, combination, 561, 573, 574, 576, 577
complex, 559
difference, 561, 577
feeling, 482, 493
fusion of, 560
masking of one by another, 562
summation, 561, 577
Tonus centers, 694, 698
gradients in intestine, 417
of cardiac centers, 303
of skeletal muscle, 691, 697
of smooth muscle, 93, 98
relation of, to posture, 693, 698
theories of, 692, 697
Total metabolism, 462, 470
Touch, 511, 519, 520
adaptation of, 524
energy to stimulate, 474
intensity of, 524
local sign of, 526
localization of, 525
projection of, 526
receptors, 480, 521, 533
sensations, adaptation of, 524
intensity of, 524, 533
local sign in, 526
localization of, 525, 534
spots, 521, 533
Toxin, 255, 266
Trephones, 64, 67, 260
Trypsin, 413, 422
Trypsinogen, 412, 422
Tuba auditiva, 552, 554
Tube, Eustachian, 552
Tubules, convoluted, functions of, 145, 151
Tunic, fibrous, 583
vascular, 585
Twitch, 81, 97
Two-point threshold, 534
Tympanic membrane, 552, 576

U

Ultra-violet radiation, 196
Unconditioned reflexes, 723, 782
Undernutrition, 468, 471
Unit circulation, 283, 308
Urea, 236, 242
formation, 183, 191
Ureters, 441, 444
Uric acid, 236
deposition of, 237
Uricase, 237
Urinary bladder, 441, 444
Urine, concentration of, 146
composition of, 147
formation, factors governing, 432
quantity of, 432, 443
reabsorption of solids from, 435, 443
of water from, 436, 444
secreted constituents of, 434, 443
specific gravity of, 432, 443
threshold substances of, 435, 443
volume, effect of circulatory changes on, 438, 444
Urobilin, 240
Utricle, 504

V

Valves of heart, 313, 315, 320, 323
Vascular tunic, 585
Vasoconstriction, 333, 339
Vasoconstrictor center, 334, 339
functions of, 336
neurons, 334, 339
Vasodilatation, 333, 339
Vasodilator center, 337, 339
mechanism, functions of, 337, 339
neurons, 334, 339
reactions, local, 338, 340
Vasomotor mechanism, 333
Veins, 290, 343, 360
valves of, 346
Venoconstrictor mechanism, 346, 361
Venous circulation, accessories to, 346, 361
pressure, 318, 343, 360

Ventilation, principles of, 384
Ventricle, 290, 312
  output of, 318
Venules, 289, 343, 360
Vibration sense, 519
Vibrissæ, 522
Villi, arachnoid, 359
Visceroceptors, 480, 495
Visibility threshold, 638
Vision, 579
  afferent tracts of, 708, 715
  binocular, 675, 686
  fusion in, 647
  spatial relations in, 660, 685
  temporal relations in, 645
Visual acuity, 606, 662, 685
  angle, 606
  perception of distance, 674, 677, 686
    of form, 673, 686
    of motion, 673, 686
  purple, 632, 684
  sensations, 634, 684
Vital capacity, 367, 371
"Vital" centers, 131
Vitamins, 55, 58, 193, 209
  "A," 63, 67, 194, 210
  "B," 194, 210
  "C," 195, 210
  "D," 196, 210
  "E," 197, 210
Vitreous body, 586, 604
  humor, 586, 604
Vocal cords, 566, 577
Voice, 564, 577
  frequency range of, 566
Volition, 731
Volume (sound), 559, 573, 574, 575, 577
Vomiting, 406, 409

W

Waking, 742, 744
Wallerian degeneration, 115, 119
Warm-blooded animals, 446, 451
Warmth receptors, 533
  spots, 480, 512, 533
Water as a factor in cell environment, 157, 169
  deprivation of, 160
  distribution of, in body, 158
  intake, 159
  intercellular, 159, 169
  intoxication, 160
  of metabolism, 157, 169
  protoplasmic, 158
Wave front (of light), 594
Weariness, 736, 743
Weber's law, 491, 497, 502
  exemplification of, in vision, 648, 684
White, sensation of, 684
Work, metabolic cost of, 463

X

Xanthin, 237
Xerophthalmia, 194, 210

Z

Zonule of Zinn, 609
Zymogen, 139, 150

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